"A STUDY ON ASSOCIATION OF BLOOD SUGAR WITH PANCREATIC ENZYMES IN OPC POISONING"

Dissertation submitted in partial fulfillment of the

Requirement for the award of the Degree of

DOCTOR OF MEDICINE - BRANCH VII

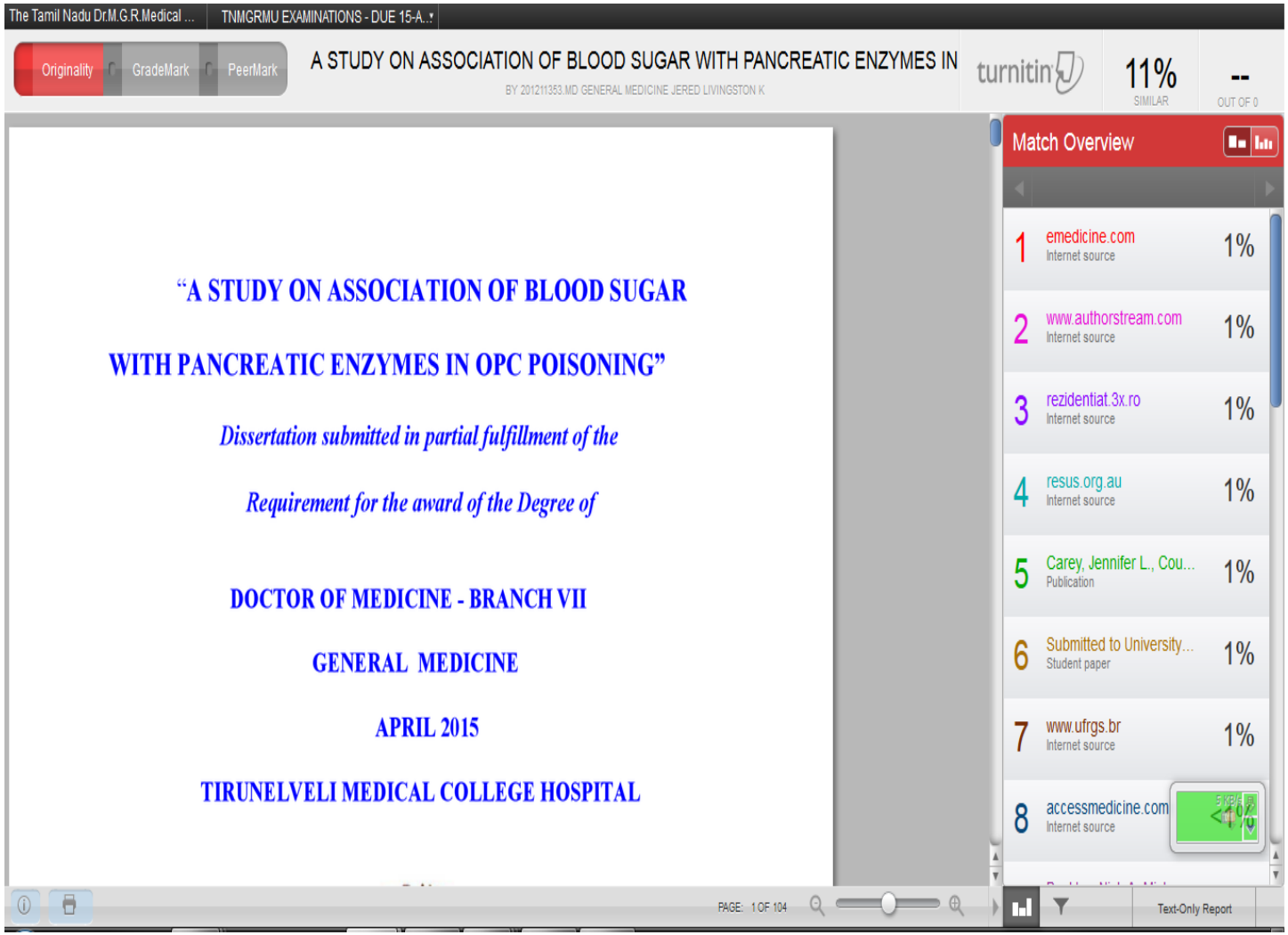
GENERAL MEDICINE

APRIL 2015

TIRUNELVELI MEDICAL COLLEGE HOSPITAL

THE TAMIL NADU DR.M.G.R. MEDICAL UNIVERSITY

CHENNAI ,TAMIL NADU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CERTIFICATE

This is to certify that the Dissertation entitled **"A STUDY ON ASSOCIATION OF BLOOD SUGAR AND PANCREATIC ENZYMES IN OPC POISONING"** submitted by **Dr.K.JERED LIVINGSTON** to The Tamilnadu Dr. M.G.R. Medical University, Chennai, in partial fulfillment for the award of M.D.Degree(GENERAL MEDICINE) is a bonafide work carried out by him under my guidance and supervision during the academic year 2012-2015. This dissertation partially or fully has not been submitted for any other degree or diploma of this university or other.

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Tirunelveli – 627011.

The Dean,
Tirunelveli Medical College,
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CERTIFICATE OF REGISTRATION & APPROVAL OF THE TIREC REF NO: 418/GM/2013/29.03.13

PROTOCOL TITLE: A Correlation of Plasma Sugar Levels and Pancreatic Enzymes in Organo Phosphorus Poisoning

NAME OF PRINCIPAL INVESTIGATOR: K.Jered Livingston

DESIGNATION OF PRINCIPAL INVESTIGATOR: Post Graduate Resident

DEPARTMENT & INSTITUTION: Department of General Medicine, Tirunelveli Medical College

Dear Dr K.Jered Livingston *, the Tirunelveli Medical College Institutional Ethics Committee (TIREC) reviewed and discussed your application during the IEC meeting held on* 29.03.2013.

THE FOLLOWING DOCUMENTS WERE REVIEWED AND APPROVED

1.	TIREC Application Form	☐
2.	Study Protocol	☐
3.	Department Research Committee Approval	☐
4.	Patient Information Document and Consent Form in English and Vernacular Language	☐
5.	Investigator's Brochure	☐
6.	Proposed Methods for Patient Accrual Proposed	☐
7.	Curriculum Vitae of the Principal Investigator	☐
8.	Insurance /Compensation Policy	☐
9.	Investigator's Agreement with Sponsor	☐
10.	Investigator's Undertaking	☐
11.	DCGI/DGFT approval	☐
12.	Clinical Trial Agreement (CTA)	☐
13.	Memorandum of Understanding (MOU)/Material Transfer Agreement (MTA)	☐
14.	Clinical Trials Registry-India (CTRI) Registration	☐

THE PROTOCOL IS APPROVED IN ITS PRESENTED FORM ON THE FOLLOWING CONDITIONS

1. The approval is valid for a period of 2 year/s or duration of project whichever is later
2. The date of commencement of study should be informed
3. A written request should be submitted 3weeks before for renewal / extension of the validity
4. An annual status report should be submitted.
5. The TIREC will monitor the study
6. At the time of PI's retirement/leaving the institute, the study responsibility should be transferred to a person cleared by HOD
7. The PI should report to TIREC within 7 days of the occurrence of the SAE. If the SAE is Death, the Bioethics Cell should receive the SAE reporting form within 24 hours of the occurrence.
8. In the events of any protocol amendments, TIREC must be informed and the amendments should be highlighted in clear terms as follows:
   a. The exact alteration/amendment should be specified and indicated where the amendment occurred in the original project. (Page no. Clause no. etc.)
   b. The PI must comment how proposed amendment will affect the ongoing trial. Alteration in the budgetary status, staff requirement should be clearly indicated and the revised budget form should be submitted.
   c. If the amendments require a change in the consent form, the copy of revised Consent Form should be submitted to Ethics Committee for approval. If the amendment demands a re-look at the toxicity or side effects to patients, the same should be documented.
   d. If there are any amendments in the trial design, these must be incorporated in the protocol, and other study documents. These revised documents should be submitted for approval of the IEC, only then can they be implemented.
   e. Approval for amendment changes must be obtained prior to implementation of changes.
   f. The amendment is unlikely to be approved by the IEC unless all the above information is provided.
   g. Any deviation/violation/waiver in the protocol must be informed

STANDS APPROVED UNDER SEAL

Dr.K.Shantaraman MD
Registrar, TIREC
Tirunelveli Medical College, Tirunelveli – 627011
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Dr.V.Ramasubramanian MD DM
Member Secretary, TIREC
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State of Tamilnadu, South India

DECLARATION

I**, Dr.K.JERED LIVINGSTON,** solemnly declare that the Dissertation titled **"A STUDY ON ASSOCIATION OF BLOOD SUGAR AND PANCREATIC ENZYMES IN OPC POISONING "** has been prepared by me.

This is submitted to the Tamilnadu Dr.M.G.R. Medical University, Chennai, in partial fulfillment of the regulations for the award of MD Degree Branch VII (MEDICINE).

It was not submitted to the award of any degree/diploma to any University either in part or in full previously.

Place: TIRUNELVELI

Date:

DR.K.JERED LIVINGSTON,

POST GRADUATE,

M.D.GENERAL MEDICINE,

TIRUNELVELI MEDICAL COLLEGE HOSPITAL

ACKNOWLEDGEMENT

At the outset I wish to thank our Dean Dr.MANOHARAN, MS, for permitting me to carry out this study in our hospital.

I express my sincere thanks to my Professor and H.O.D DR.VAIRAMUTHU RAJU.MD, for his support and encouragement throughout the study.I am also deeply indebted to my chief Prof DR.PAULRAJ.MD ,who was the main motivator behind the study.I would also like to thank Prof DR. VAIRAMUTHU RAJU.MD, who suggested the topic and was the brain behind the topic.

I am thankful to my assistant professors DR.RATHNAKUMAR.MD, and DR.JAWAHAR.MD, for their valuable suggestions.

I also thank my former assistant professors DR.MANMADHARAJA.MD, DR.MOHAMMADRAFI.MD, DR.RAVI.MD and DR.RENUGA.MD, for their encouragement and valuable guidance to the study.

I am also immensely grateful to my statistician, Mr.SELVAPRAKASAM,for the guidance provided in the analysis and interpretation of the data.

I also thank the Departments of Microbiology,Pathology and Biochemistry, for the laboratory support to this study.

Last but not the least, I sincerely thank all the patients and their parents who cooperated with me by participating in the study.

CONTENTS

ABSTRACT

BACKGROUND:

Aim of this study is to know the prevalence of hyperglycemia in OPC poisoning ,to know the prevalence of pancreatitis in OPC poisoning and to find the association of hyperglycemia and elevated pancreatic enzyme level.

STUDY METHOD:

The study was conducted in Tirunelveli medical college,intensive medical care unit in 100 patients who consumed OPC, excluding alcoholic, diabetic,patients who underwent pancreatic procedures.It is a cross-sectional study.In this study serum amylase is compared with variables such as age,sex, vitals,compound,amount,blood sugar, WBC,PCV,lipase.The results were analysed and interpreted using software by statistician.

CONCLUSION:

Among 100 patients studied , serum amylase were elevated in 6 patients. Serum lipase were elevated in 6 patients. Blood sugar were elevated in 10 patients.Among patients with hyperamylasemia only 2% have elevated blood sugar.So, correlation between blood sugar and serum amylase still have to be

studied.Hyperglycemia in OPC is due to initial hypoglycemia or due to pancreatic insufficiency.In our study their relation is not statistically significant.

KEYWORD:

OPC,pancreatitis, amylase,lipase,blood sugar.

INTRODUCTION

A poison is a substance which on inhalation, ingestion, or with direct contact produces deleterious or harmful effect on human being.

POISONING:

Accidental and suicidal poisoning remains the major worldwide problem which results in significant annual morbidity and mortality.. In general,decontamination followed by supportive care has been regarded as essentials of clinical poisoning management. However in certain circumstances specific antidotes reduce the, morbidity and mortality and duration of hospitalisation.

Establishment of toxicology response centre is a emerging need in India. Antidotes were considered essential and necessary within the first hour of patient presentation .The quantity of antidote recommended is based on the dose necessary to treat one or two 70 kg man.As per BAEM (british association of emergency medicine) guidelines for stocking the antidotes should be divided on the basis of immediate availability and andidotes that should be available within 4 hours of admission.

OPC POISONING:

Organophosphorus compound(OPC) is commonly available in almost all parts of

India.It kills an estimated population of 200 000 people every year. Commonly consumed organophosphorus compound in this part of state are monocrotophos, propophenos, and dimethoate.Each of these compounds have different toxicity index so that their lethal dose varies. Each of these compound known to produce complications other than usual features suggestive of cholinergic action on muscarinic and nicotinic receptors. Usually these patients admitted in intensive medical care unit with neurological and respiratory symptoms. Pancreatitis is a known but rare complication , often goes unrecognised. So, high suspicious eye is essential to identify these patients presenting with unexplained hemodynamic instability.

Metabolic complications such as hyperglycemia, diabetic Ketoacidosis have to be kept in mind.There are certain scales to assess the need for mechanical ventilation, dose of atropine called peradineya scale which is based on features such as, miosis,bradycardia respiration,fasciculation and level of consciousness. In this study I am going to correlate the association of blood sugar with pancreatic enzyme levels.

AIM & OBJECTIVE:

- To know the prevalence of hyperglycemia in OPC poisoning
- To know the prevalence of pancreatitis in OPC poisoning
- To find the association of hyperglycemia and elevated pancreatic enzyme level

REVIEW OF LITERATURE:

OPC is most popular and widely used insecticide in india. It is consumed as either suicidal or unintentional as in case of occupational exposure.These compounds are available as dusts, granules, or liquids.Toxicity profile varies for different compounds. Also the toxokinetics varies depends on the route of administration such as transdermal , trans conjunctival, inhalational through mucosa of respiratory tract, gastrointestinal tract.

It was used as bio weapon in 1995 tokyo subway attack. Nerve agents used was sarin.Because of its increased use and its popularity incidence of poisoning is also high.Severity of poisoning depends on various factors such as type of compound, amount, route of exposure and time taken to treat the patient.

Increased incidence is noted in men because of work- Related exposure and increased suicidal attempts.Common cause of mortality is respiratory failure followed by cardiac events.Also contributed by unnoticed complication so called acute pancreatitis As evidenced by studies conducted in Yuuncu Yol University which includes 159 patients of which 36% percent showed hyperamylasemia.Among them one-third have elevated lipase levels.

Dressel and colleagues have one experiment in dogs about anti-cholinesterase induced pancreatitis secondary to stasis of exocrine secretions. From a case report from University of Manitoba it is shown that 7% of patients shows hyperglycemia .14% percent shows glycosuria, paradoxically hypoglycemia is also reported.

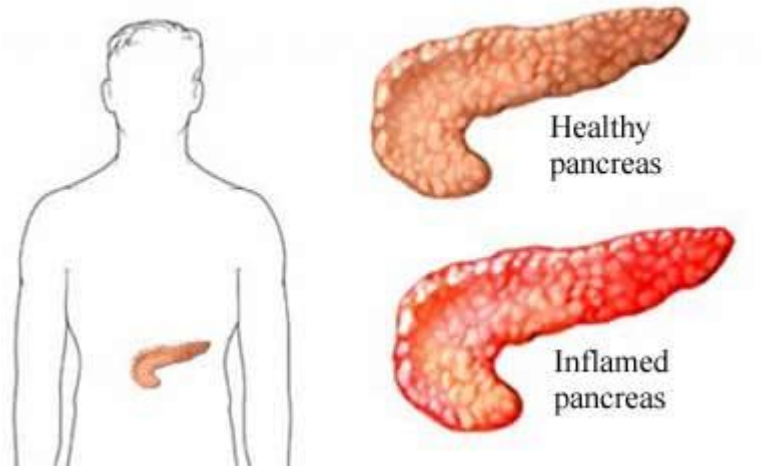
This effect is either due to insulin secretion by cholinergic stimulation or whether the hyperglycemia in OPC is due to secondary hormonal effects to hypoglycaemia or due to necrosis of pancreas, is still unclear.

ABOUT PANCREAS:

ANATOMY OF PANCREAS:

Pancreatitis is the pathology characterised by inflammation of pancreas.As the common bile duct and pancreatic duct have common pathology, either pancreatic enzymes or bile can reflux into the above ducts and cause theorgan damage. Gall stone is the common implicated culprit followed by Alcohol, toxins and drugs.

It can lead to various secondary pathological changes due to near by association of superior mesenteric artery, vein, and bowel structures.It causes aneurysm of superior mesenteric artery, thrombosis of superior Mesenteric vein and ischemia of surrounding bowel loops. So it can lead to rupture of artery and torrential bleed and hemodynamic compromise.



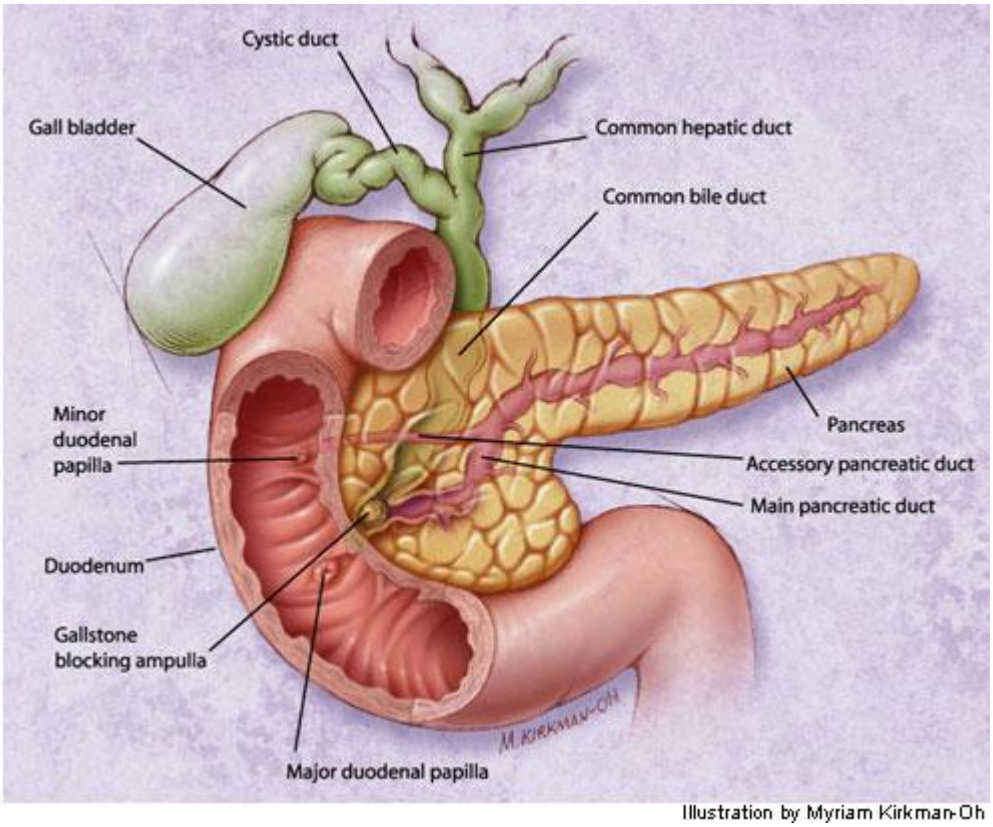
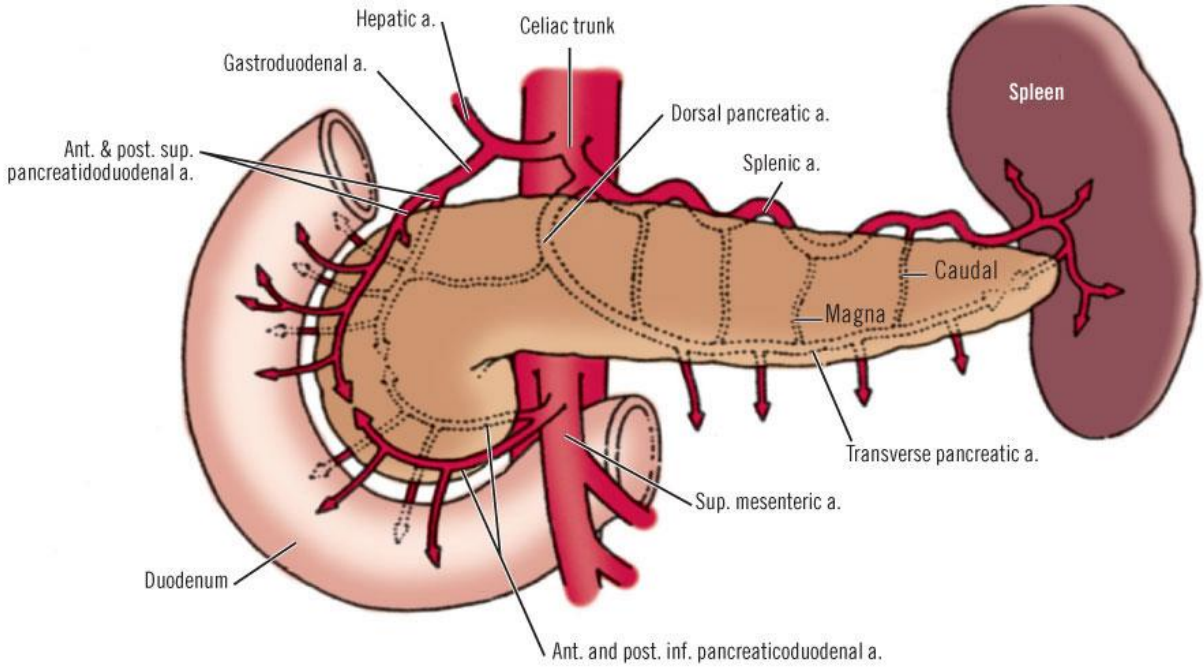


Illustration by Myriam Kirkman-Oh

As pancreas is a retro-peritoneal organ , bleeding from it can track either anterior to thoracolumbar fascia and perirenal fascia and appears as Cullens sign around the umbilicus. On the other way it can track through lesser omentum , to appear as Grey-Turners sign near flanks..

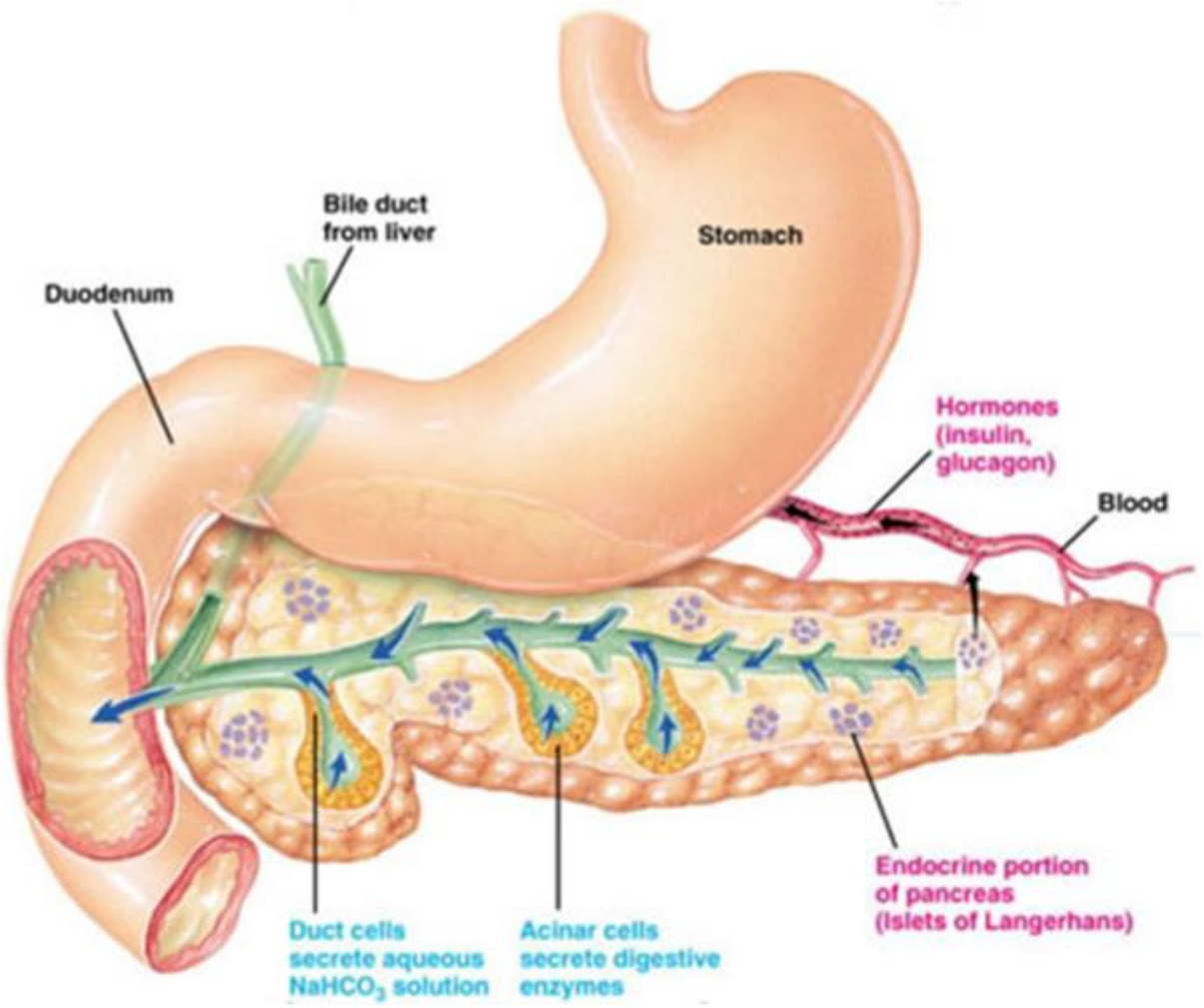
Due to close relation to stomach any inflammation in and around pancreas can cause stasis and vomiting due to involvement of superior mesenteric plexus, which contributes autonomic supply , that explains paralytic ileus in pancreatic inflammation.In severe to chronic cases , fluid accumulates around the pancreas that leads to collection of fluid called as pseudocyst.



FUNCTIONS OF PANCREAS:It weighs about 70gm in adult male and 66gm in adult female It has both endocrine and exocrine function.It helps in digestion of fat. Islets of Langerhans are the functional unit of Pancreas. They secrete four polypeptide hormones like insulin, glucagon, somatostatin,and pancreatic polypeptide.They help in the metabolism of carbohydrates, proteins and fat.Per day healthy adult secretes around 35-100 units…

REGULATION OF PANCREATIC SECRETION:

The exocrine pancreas is influenced by both hormonal and neural systems. Secretin is secreted from duodenum evoked by gastric acidity.

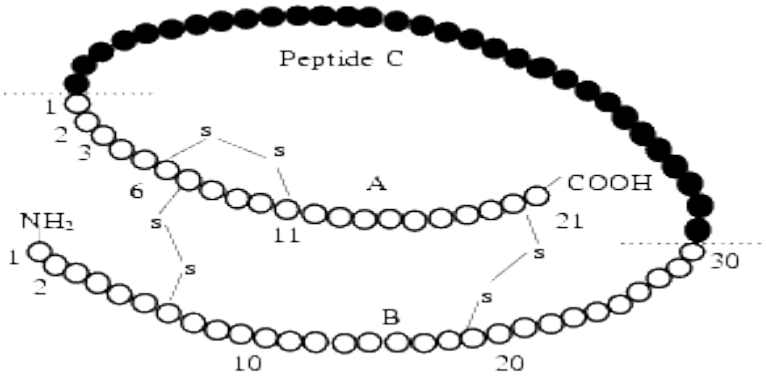


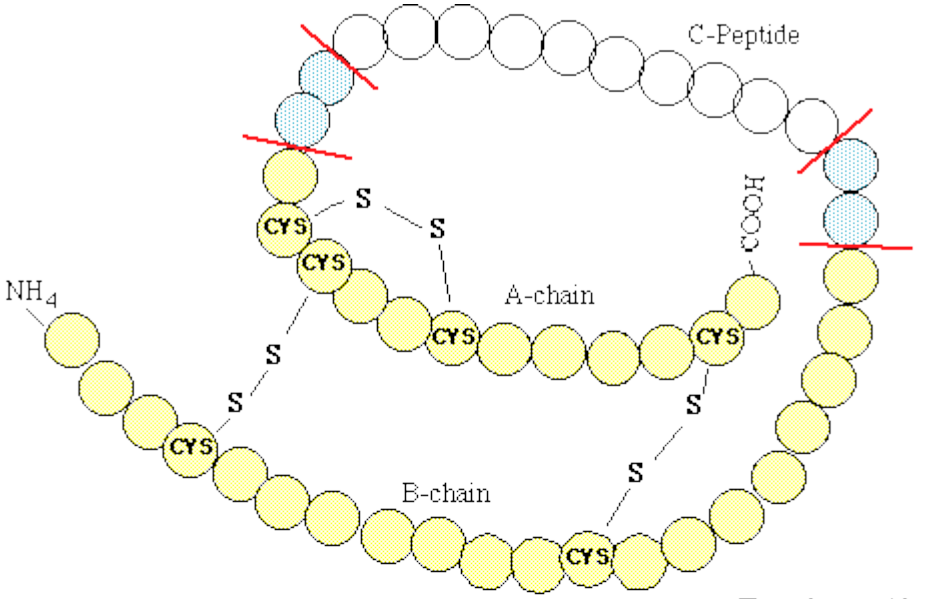
It controls the bicarbonate rich secretion from the pancreas. CCK controls the enzyme rich secretion which is evoked by the long chain fatty acids , essential amino acids.The parasympathetic nervous system have afferent and efferent through Vagus that controls mainly the enzyme rich secretion .Hormonal effects mainly control the bicarbonate rich secretion.

Vagal stimulation causes release of vasoactive intestinal peptide (VIP),secretin agonist. Pancreatic exocrine secretion is mediated by inhibitory neuropeptides such as somatostatin, pancreatic polypeptide, peptide YY, neuropeptide Y, enkephalin, pancreastatin, calcitonin gene–related peptides, glucagon, and galanin.

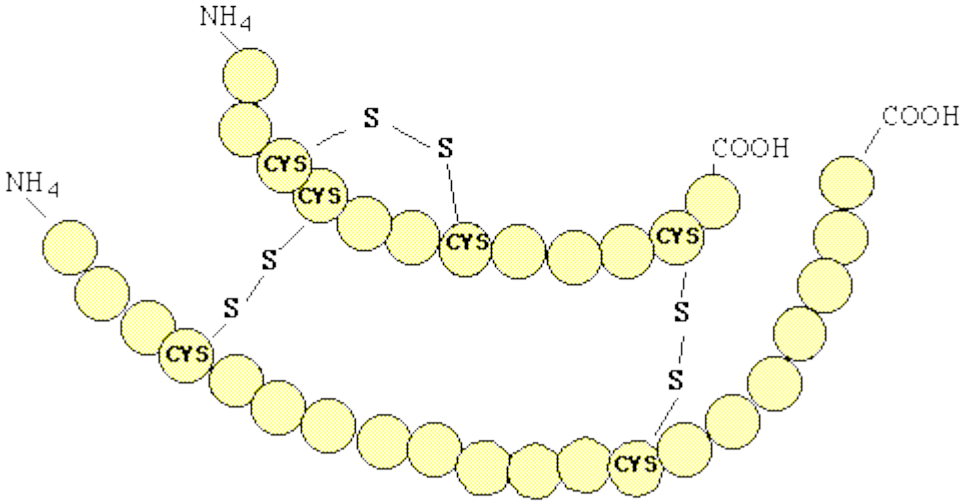
Water and Electrolyte Secretion:

Bicarbonate is the anion which is a physiological buffer. The ductal cells concerned with secretion of bicarbonate which is predominantly (93%) derived from plasma. Bicarbonate gain entry through sodium bicarbonate- chloride exchanger which is mediated by CFTR channel(cystic fibrosis transmembrane regulator) through which chloride efflux occurs during depolarisation.Bicarbonate secretion is augmented by secretin.It neutralize the acid PH and create environment for absorption of bile salt and fatty acids.





Proinsulin



Insulin

Enzyme Secretion

The acinar cell secrete enzyme rich fluid and highly compartmentalised. The pancreas secretes amylolytic, lipolytic, and proteolytic enzymes. Amylase an amylolytic enzyme, breaksdown starch to oligosaccharides and to the disaccharide maltose.Lipase,phospholipase A2, and cholesterol esterase comes under lipolytic enzymes. Bile salt stimulates phospholipaseA2 , cholesterol esterase, but inhibit the lipase which is hampered by co-

lipase. Proteolytic enzymes are secreted in inactive form as zymogen includes both exopeptidase and endopeptidase .Exopeptidase includes aminopeptidase and carboxypeptidase that cleaves N- terminal amino group and C-terminal carboxyl group respectively. Endopeptidase cleaves the internal bond formed between nucleic acid Enterokinase, duodenal mucosal enzyme that breaks the lysine- isoleucine bond of trypsinogen to form trypsin. Trypsin stimulate other proteolytic enzymes. To summarise,all pancreatic enzymes are activated in alkaline PH. Neural control plays major role in mediating the enzyme rich secretion.

Autoprotection of the Pancreas

Autodigestion of the pancreas is hampered by the compartmentalised pancreatic proteases in inactive form and by the synthesis of protease inhibitor.These protease inhibitors are found in the acinar cells, the pancreatic secretions, and globulin1 and2 fractions of plasma.

Tests useful in diagnosis of pancreatic disorders:

More than 90% of the pancreas must be damaged before the symptoms of exocrine insufficiency manifests.

Noninvasive tests of pancreatic exocrine function such as fecal elastase are abnormal in patients with obvious pancreatic disease than in patients with occult disease.

Test pertaining to pancreatic enzymes:

Serum amylase and Serum lipase.

Amylase can be tested in serosal cavity collections such as pleural fluid and ascitic fluid.

It is not specific as non- pancreatic disorders can also show hyperamylasemia and so many false positive results can occur.

Tests pertaining to pancreatic structure:

Includes both invasive and non-invasive radiographic techniques.

Plain film of abdomen shows calcification if any.

Ultrasonogram – can show any fluid collection , mass, pseudocyst.

CT – abdomen- clear anatomical description of pancreas including the ductal system.

ERCP(endoscopic retro-grade cholangio pancreatogram)

MRCP(magnetic resonance cholangio pancreatogram)

Endoscopic ultrasonogram ,CT- guided pancreatic biopsy

Tests for exocrine function:

Analysis of duodenal contents:

Secretin-pancreozymin-CCK test, Endoscopic secretin –CCK test

Examination of intraluminal products of digestion:

Microscopic examination of stools for digestive products of fat

Quantitative analysis of fat ,Fecal nitrogen and elastase

Pancreatic enzymes in body fluids:

The serum amylase and lipase levels are used as screening tests for suspected acute pancreatitis. Three fold rise of enzymes clinch the diagnosis excluding bowel perforation . Within 24 hours of onset of pancreatitis the enzymes will elevate and remains for 3–7 days. Levels usually return to normal within 7 days unless there is pancreatic ductal obstruction, or pseudocyst formation. The values may be normal if there is delay in collection of sample, or chronic pancreatitis or elevated triglyceride levels.

The serum amylase can be elevated in other non- pancreatic conditions like diseases of salivary glands, fallopian tubes, lung, thyroid, and tonsils and various other tumors.

Causes of hyperamylasemia:

Pancreatic disorder: Acute and chronic Pancreatitis. Complications of pancreatitis such as Pancreatic pseudocyst, pancreatic ascites , pancreatic abscess, pancreatic necrosis, pancreatic trauma and Pancreatic carcinoma..

Non-pancreatic disorders:

Renal insufficiency , Salivary gland lesions such as parotitis caused by Mumps and Calculus."Tumor" hyperamylasemia - Carcinoma of the lung , Carcinoma of the esophagus , breast carcinoma, ovarian carcinoma , burns, Diabetic ketoacidosis, Renal transplantation , Cerebral trauma and drugs such as morphine.

Other Abdominal Disorders

Biliary tract disease like cholecystitis, choledocholithiasis. Intraabdominal disease like perforated or penetrating peptic ulcer. Intestinal obstruction or infarction, Ruptured ectopic pregnancy Peritonitis, Aortic aneurysm, Chronic liver disease, Postoperative hyperamylasemia.

Acute Pancreatitis:

Pancreatic inflammatory disease may be classified as (1) acute pancreatitis or (2) chronic pancreatitis. The pathologic spectrum of acute pancreatitis varies from interstitial pancreatitis, milder form, to necrotizing pancreatitis , severe form.

Common Causes

Gallstones (including microlithiasis) ,Alcohol (acute and chronic alcoholism) Hypertriglyceridemia ,Endoscopic retrograde cholangiopancreatography (ERCP) Trauma (especially blunt abdominal trauma) Postoperative (abdominal and non abdominal operations), Drugs (azathioprine, 6-mercaptopurine, sulfonamides, estrogens, tetracycline, valproic acid, protease-inhibitors), Sphincter of Oddi dysfunction.

Uncommon Causes

Vascular causes and vasculitis (ischemic-hypoperfusion states after cardiac surgery) Connective tissue disorders and thrombotic thrombocytopenic purpura (TTP) ,Cancer of the pancreas, hypercalcemia ,Periampullary diverticulum , Pancreas divisum ,Hereditary

pancreatitis Cystic fibrosis and Renal failure .

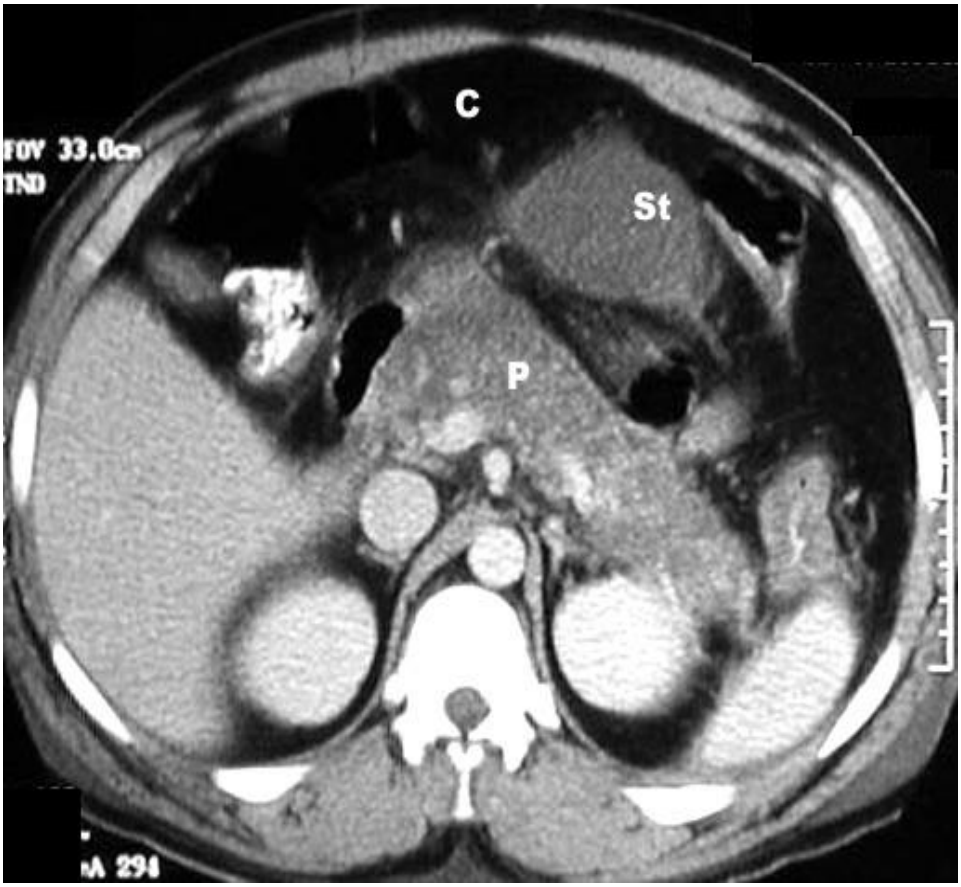
Rare Causes

Infections (mumps, coxsackievirus, cytomegalovirus, echovirus, parasites)

Autoimmune (e.g., Sjögren's syndrome)

Clinical features:

Abdominal pain is the major symptom of acute pancreatitis.Pain characterised by steady and boring in character, is located in the epigastrium and periumbilical region and often radiates to the back.The pain is frequently more intense when the patient is supine, sometimes relieved by sitting and bending forward .low-grade fever, tachycardia, hypotension ,and shock. Jaundice occurs infrequently; when present, it is usually due to edema of the head of the pancreas with compression of the intrapancreatic portion of the common bile duct. Erythematous skin nodules due to subcutaneous fat necrosis. Pulmonary findings, includes basal crackles, atelectasis, and left sided pleural effusion commonly. Grey turner and cullens sign are uncommon, indicate the presence of a severe necrotizing pancreatitis.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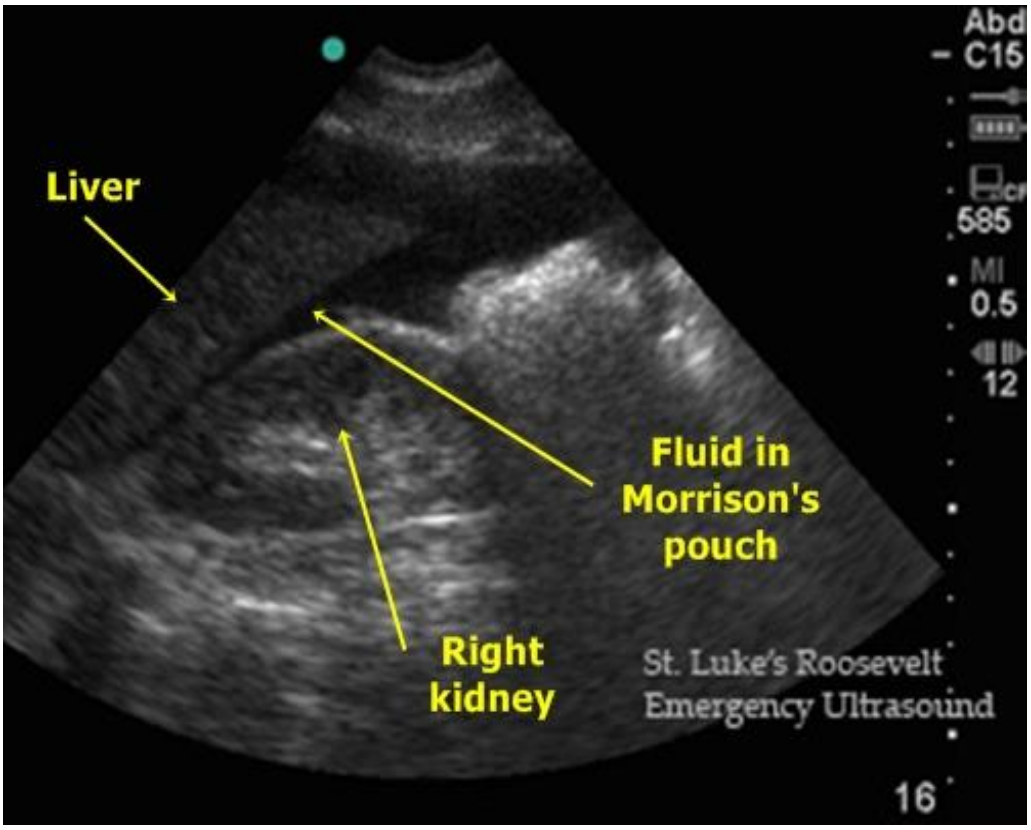
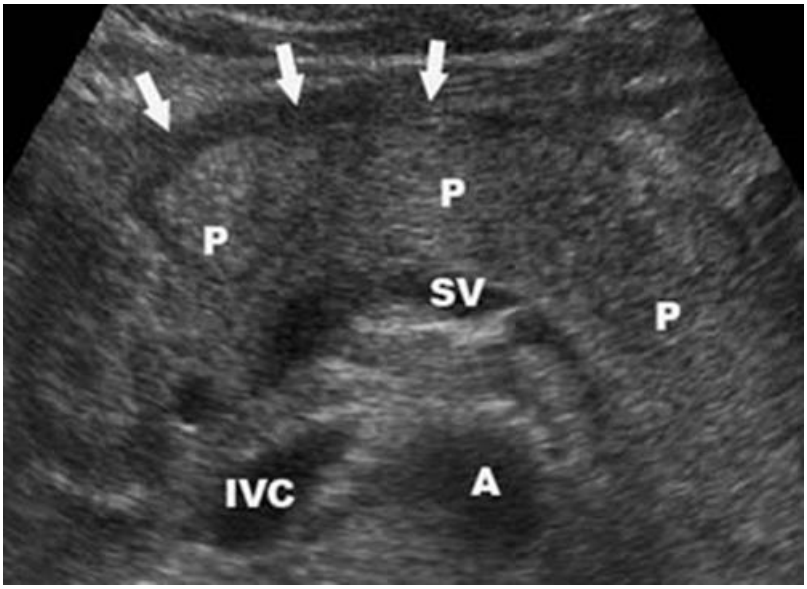
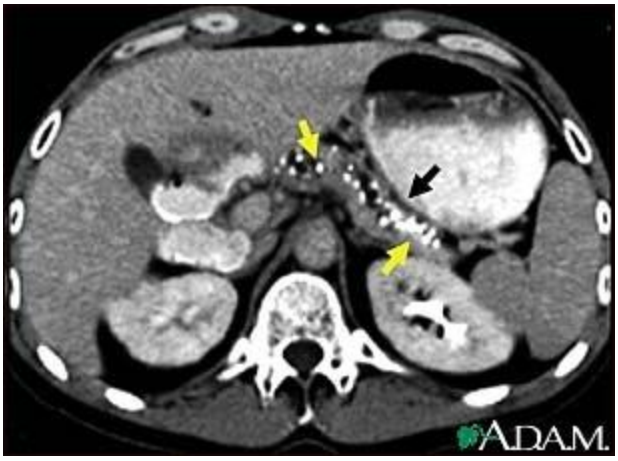

Liver
Fluid in Morrison's pouch
Right kidney
St. Luke's Roosevelt Emergency Ultrasound
16
Abd
C15
585
MI
0.5
12



Laboratory evidence:

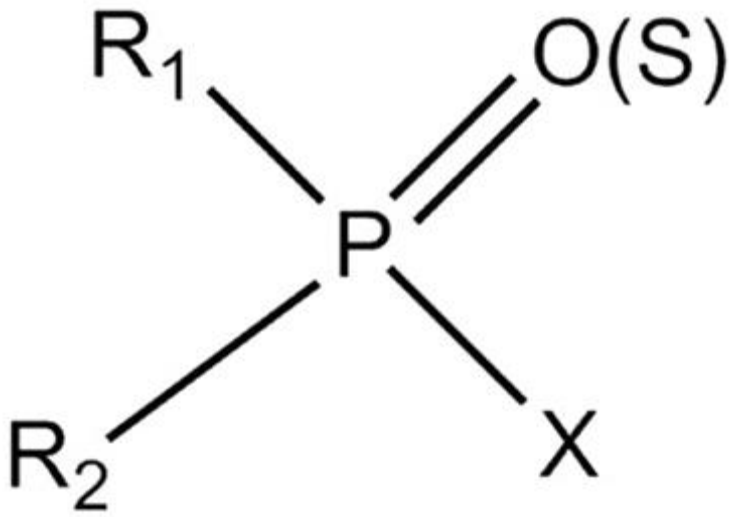
Leucocytosis, azotemia, hyperglycemia, hypertriglyceridemia, hypocalcemia,

raised haematocrit, hyperbilirubinemia ,hypoxemia, ST-T changes in ECG.



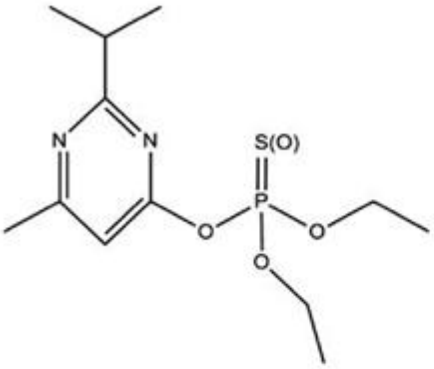
STRUCTURE OF OPC:

Most commercially used OPC contain pentavalent phosphorus linked to oxygen by a double bond , two variable groups R1 and R2. X is an ester linked arrangement which is also called leaving group , that is easily hydrolysed when OPC combines with the enzyme.

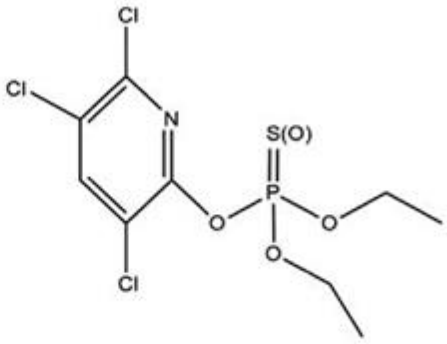


Instead of oxygen atom if there is sulphur atom it is organophosphorothiates. It has to be converted to oxon derivatives by microsomal enzyme p450 so that they inactivate the enzyme more potentially.

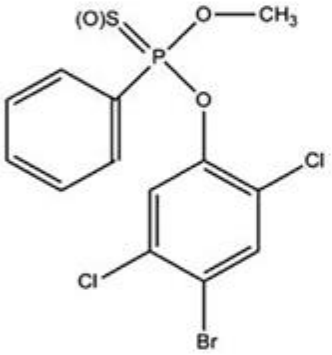
Structures of typical organophosphates



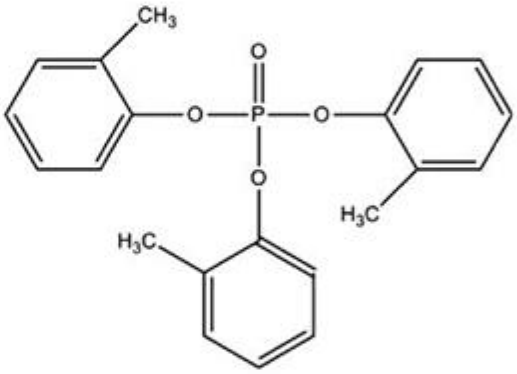
Diazinon



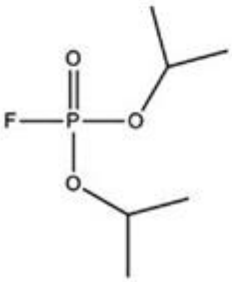
Chlorpyrifos



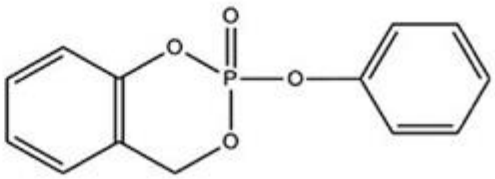
Leptophos



TOCP



DFP



Phenyl saligenin phosphate

TOXICOKINETICS:

Absorption: It is proportional to contact time with skin. Also it depends on lipid solubility and nature of solvent, permeability of clothing, volatility, finest nature, if it is in powder form. Also absorption depends on area of skin for example more absorption takes place in scrotal skin, axilla, skin of head and neck than skin of hands, also traumatised skin

dermatitis favours the absorption.

Distribution & storage:

Generally OPC are lipophilic, and cross the blood brain barrier. The phosphorothioates (P=S), for example diazonin, parathion, and bromophos, are more lipophilic than phosphates (P=O).So they are stored in fat, liver, kidney, and salivary glands. This may be reason for prolonged toxicity and relapse after recovery.

Bio-transformation:

OPC such as phosphorothiotes have to be activated to oxons by monooxygenase system mediated by P-450 isoforms. It is a combination of oxidation and desulfuration reaction. Whereas phosphates are biologically active and its action is immediate but, thioates actions are delayed.These oxons are deactivated by hydrolases.

Elimination:

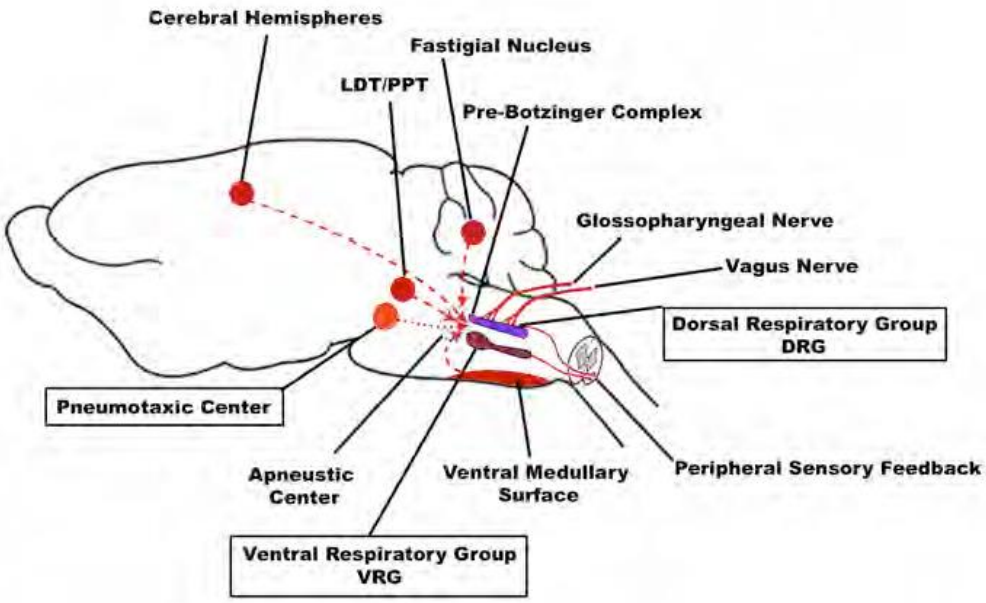
Mainly through urine also through faeces.Compounds such as diazinon are eliminated within hours whereas others will take days as they are stored in fat.

OPC & respiration:

Respiratory neurons are located in medulla and pons as three groups.The dorsal respiratory group in the medulla is located in the nucleus tractus Solitarius. The ventral respiratory group is located in the ventrolateral medulla and is divided into three regions,

caudal, intermediate and rostral. The rostral ventral respiratory group contains the pre-Botzinger complex. The pontine respiratory group (also called the pneumotaxic center) is located in the nucleus parabrachialis medialis and the Koliker-Fuse nucleus.

HERING-BREUR reflex mediated by activation of stretch receptors that lead to temporary cessation of respiration. Cough reflex is also initiated through same mechanism , that is mediated through C- fibres. Fluid in alveoli will stimulate the J- receptors that cause reflex tachypnoea.



Pulmonary activities are mediated by post-junctional effects of acetylcholine. Acetylcholine is accumulated in synaptic vesicles at the post-synaptic nerve terminals and depolarization of the nerve terminal causes release of acetylcholine into the synaptic cleft, where it diffuses

to interact with both pre- and post-synaptic receptors.. Two cholinergic mechanisms modulate pulmonary vascular tone, a direct stimulatory effect and an indirect endothelium dependent(nitric oxide) relaxing effect. Acetylcholine also inducesbronchial smooth muscle constriction, regulating bronchial airflow narrowing the airway diameter. Airway smooth muscle contraction is induced by muscarinic receptors (M2 and M3).Bronchospasm is a common complication of acute OP poisoning. Stimulation of sympathetic fibers causes relaxation of bronchial smooth muscle while stimulation of parasympathetic fibers causes bronchoconstriction. Efferent signals carried by vagus mediated by substance P and acetylcholine results in bronchospasm.Effects from a variety of local compounds mediate changes in bronchial tone with compounds such as acetylcholine, histamine, serotonin, leukotrienes, adrenergic agonists and others mediating bronchoconstriction and compounds such as ß2-agonists, nitric oxide, and others mediating bronchodilatation.OP causes alteration in diffusion capacity through various mechanisms. One among them is altering the calibre of pulmonary vasculature.

Pooling of pulmonary secretion in OPC poisoning is mediated by both local causes and neurogenic causes. Respiratory failure in OPC poisoning occurs through two mechanisms: central apnea and pulmonary dysfunction mediated by vagus nerve.

As per one study, after vagotomy the central mechanism for respiratory control

ceases and that leads to hypoventilation further leads to apnoea. As per another study conducted in animals ,vagal denervation interrupts the efferent signals from bulbar nucleus to lungs that leads to defect in alveolar level.The effects of OP in cardio-vascular system includes variation in blood pressure, pulse rate, various types of arrhythmias and it does not correlate withpulmonary diffusion capacity and central apnoea.

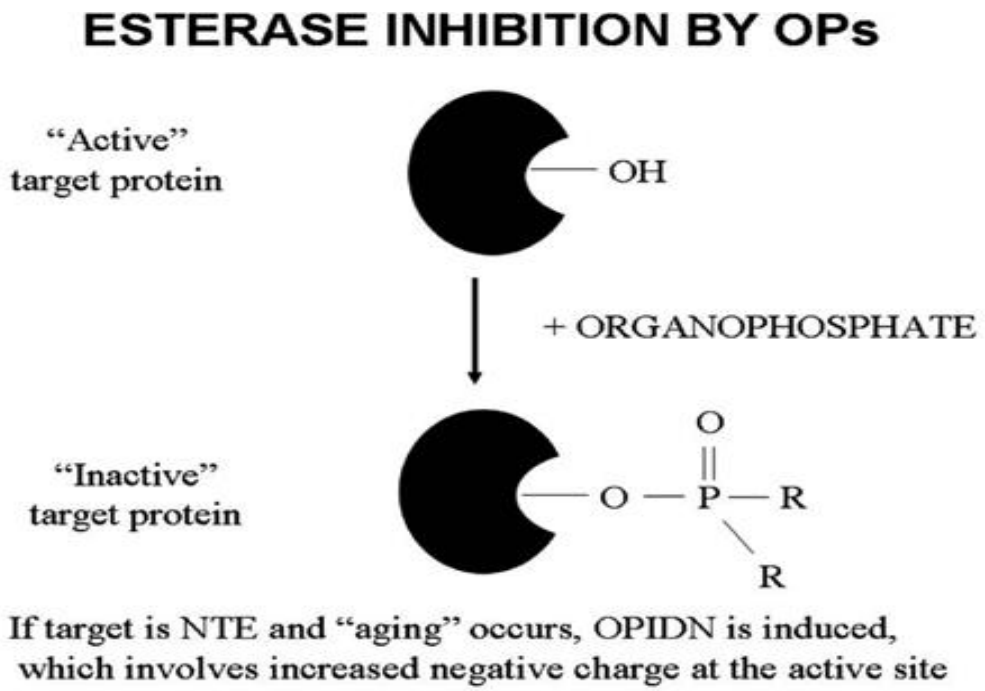
OP has both central effects and direct effects in heart. Stimulation of vagus cause constriction of bronchial smooth muscles and dilatation of pulmonary vasculature that leads to ventilation-perfusion (V-Q) mismatch. These changes collectively increase the arterial – alveolar gradient in OPC poison.

MECHANISM OF ACTION & PATHOPHYSIOLOGY:

OPC acts by binding to active site of acetylcholine esterase by stereotypic inhibition .The signs and symptoms is due to acetylcholine excess in neuromuscular junction.It has both muscarinic and nicotinic actions.It acts on post ganglionic parasympathetic secretory glands, smooth muscles of respiratory tract, gastro-intestinal tract, bladder, eye, and heart. Also it acts on post ganglionic sympathetic sweat glands leading to constellation of signs and symptoms such as increased secretion in lungs, and so on.

It acts on nicotinic receptors leads to persistent depolarisation. Also it crosses the blood-brain barrier leads to CNS depression for reasons unknown. OPC also binds to RBC

cholinesterase and plasma cholinesterase, but the clinical effects were not explained. Its action is irreversible which is explained by process called ageing in which the phosphorylated enzyme loses the alkyl side chain non-enzymatically.The rate of hydrolysis of OPC- enzyme complex is more when compared to acetyl choline- enzyme complex as the former conjugate is relatively stable and resistant to hydrolysis, so it takes weeks to days for the enzymes to recover.



Apart from acute complications , there are certain delayed neurological manifestations which is explained by non- cholinergic Target sites such as NTE(neuropathy target esterase). It also causes disorganisation of membrane, cyto-skeleton, interrupts the protein phosphorylation, cell turn over, and affects various signalling pathways,so that it affects the

neuronal proliferation,survival.

It also interacts with non-esterase protein called tubulin.It also causes mitochondrial dysfunction, lipid peroxidation,Protein misfolding, affect ubiquitin- dependent pathway ATP- depletion,, so that it affects the ATP dependent process such as axon transport essential for nerve regeneration.

Binding to NTE may affect both its channel role in the endoplasmic reticulum and its lipid hydrolase activity, causing disruption of membranes with potential Ca2+ release, membrane cleavage and cell death.

MOLECULAR TARGETS OF OPC:

Neuropathy target esterase (NTE):

NTE is a membrane protein located in smooth endoplasmic reticulum able to conduct ions is stored in vesicles.. OPCs that are able to induce aging of NTE capable of blocking ion-conductance thus leading to OPIDN. Also it has lipid hydrolase activity, phosphotidyl choline as a substrate. It plays a role in the regulation of phospholipid turnover in cell membranes.NTE sequence is similar to swiss cheese protein (SWS)in drosophila Melanogaster,, so mutation of SWS sequence can lead to neuropathy.This degenerative condition associated with wrapping of glial cells, apoptosis of neurons, dysregulation of phospholipids. As per Glynn Proposal inhibition and aging of NTE will affect the NTE

related function such as lipid hydrolysis or ion-channel activity.NTE mutants with diminished esterase activity leads to motor neuron disease.

Role of NTE in neuronal differentiation:

Exposure of differentiating neuroblastoma cells to OPIDN inducing OP , like PSP(phenyl saligenin phosphate) will reduce the growth of axon like process. Some studies shows that knocking of NTE in differentiating SH-SY5Y cells does not affect the neurite growth. This suggest that there is some other factor other than NTE is involved in neurite growth.By one study the increased expression of NTE will cause mitotic arrest in renal cell line.

Other targets:

Cyto-skeletal proteins:

TOCP exposure will cause hyperphosphorylation of cyto-skeletal proteins.Histo-pathology shows aggregation of neuro-filament heavy chain before the development of OPIDN. As per one study however, PSP exposure in differentiating N2a cells is found to cause increased activity of the mitogen activated protein MAP kinase for which NFH is a substrate this agent was able to affect cytoskeletal integrity by disruption of signalling pathways associated with neuronal cell differentiation and survival. Neurite inhibition was associated with increased levels and phosphorylation of the actin binding protein cofilin.Cofilin regulates the dynamic properties of the microfilament network.

Proteolytic enzymes:

Wallerian degeneration is due to calcium influx , activation of calcium dependant calpain. Calpain‑mediated proteolysis of cytoskeletal proteins such as neurofilaments is an early event in OPIDN.This is evident by using calcium channel blockers in treating symptoms of OPIDN. Another inducer of OPIDN other than calpain for example,diisopropylphosphorofluoridate (DFP) is also involved in axonal degeneration.Apart from this major pathway affected is ubiquitin- dependant pathway which is involved in protein folding.so disruption of this pathway leads to protein misfolding &aggregation..

Mitochondria:

Impairment in the activity of a range of key mitochondrial enzymes such as succinate dehydrogenase, NADH dehydrogenase and cytochrome oxidase. Such that it disrupt the energy metabolism, respiratory chain, disruption of transmembrane potential, leads to depletion ATPs thus leads to apoptosis.

OTHER POTENTIAL 'NON‑ESTERASE' OPC BINDING PROTEINS

Other than AChE, NTE and other serine hydrolases alternative OP binding sites are tyrosine and lysine residues. OPC binding to albumin was detected by mass spectrometry and of prognostic significance.Chlorpyrifosoxon disrupts microtubules by preventing

polymerisation. Further analysis by mass spectrometry demonstrated the covalent interaction of chlorpyrifos with tyrosine residues in tubulin.This explains the developmental defect after exposure to OPC.

The degree of organophosphate intoxication:

Grade 0: No clinical signs or symptoms

Grade 1: increased secretion, twitching, normal level of consciousness

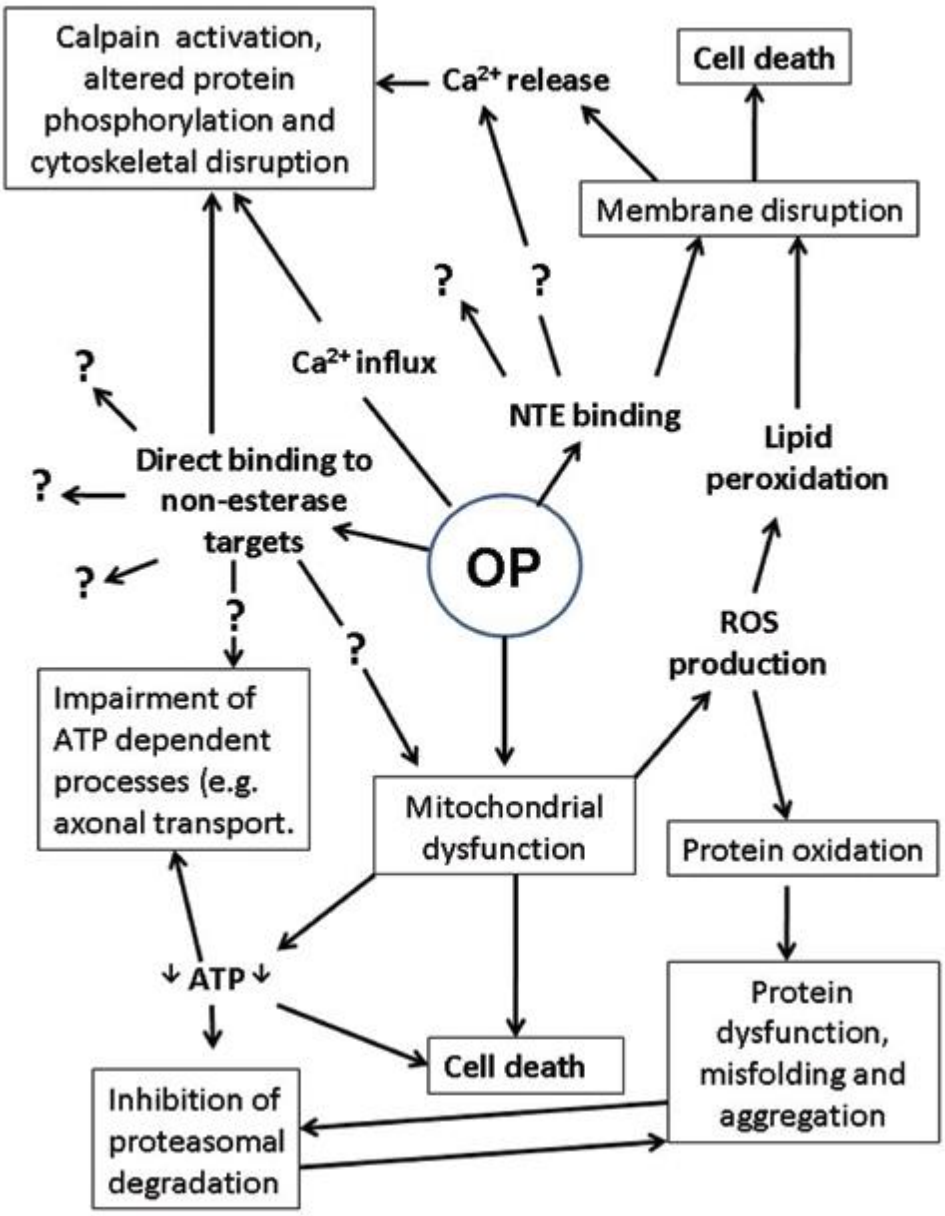
Grade 2: Grade 1 + hypotension, loss of consciousness

Grade 3: Grade 2 + not responding to noxious stimuli , chest X-ray showing features suggestive of ARDS , pO2< 10 mmHg.

ACUTE TOXICITY OF OPC:

Diarrhea/ abdomen pain--- muscarinic stimulation of colonic non-striated muscle and decreased water absorption .Micturation—muscarinic stimulation of detrusor.Miosis--- cholinergic stimulation of sphincter pupillae causing constriction of pupil .Bradycardia ---- vagal stimulation of muscarinic receptors or reflex bradycardia from increased sympathetic nerve activity.Tachycardia---- cholinergic stimulation of receptors in the sympathetic ganglia and adrenal medulla with release of catecholamines..

Non-cholinergic pathways of OP toxicity



Bronchorrhoea/Pulmonary Secretions---cholinergic stimulation of pulmonary goblet cells and glands or reflex bronchorrhea from pulmonary afferent activity via the nucleus of the solitary tract.Bronchoconstriction--- cholinergic stimulation of bronchial smooth muscle or reflex bronchoconstriction from pulmonary afferent activity via the nucleus of the solitary tract.Emesis--- cholinergic stimulation of stomach smooth muscle and gastric secretion via muscarinic receptors as well as brainstem triggered "motion sickness" with nausea and vomiting.Lacrimation--- cholinergic stimulation of lacrimal glands.Salivation ----cholinergic stimulation of salivary smooth muscle and exocytotic secretion. Fasciculations ----nicotinic stimulation of skeletal muscle fibers.

Summary :

Muscarinic receptors:

Decreased heart rate,bronchospasm, bronchorrhoea,decreased blood pressure, diarrhoea, abdominal cramps, constricted pupils and increased salivation.

Nicotinic receptors:

Increased heart rate, increased blood pressure in 20% ,fasciculation, striated muscle necrosis.

Both central muscarinic and nicotinic receptors:

Tremor, loss of coordination, seizures, respiratory depression, coma, and death.

INTERMEDIATE SYNDROME:

Occurs during one to four days after exposure,characterised by respiratory paralysis, weakness of flexors of neck, proximal limb muscles, cranial nerve palsy, opthalmoparesis. Due to inadequate treatment or delayed treatment..

OP‑Induced Delayed Neuropathies (OPIDN):

OPIDN is a neurodegenerative condition that affects long tract in both central and peripheral nervous system,characterised by delayed onset of symptoms from exposure to OPC. Symptoms starts by sensory disturbances in the form of numbness, paraesthesia in lower limbs associated with cramps followed by ascending type of flaccid motor weakness, with hyporeflexia with or without bladder and bowel disturbances ,loss of balance, steppage- gait. Brisk reflexes with spasticity supervenes during recovery, in the form of hyper reflexia, spastic gait and increased motor tone.

Lipid soluble OPC such as fenthion may produce extra-pyramidal symptoms like dystonia, cog- wheeling, tremors.Peripheral delayed sensory- motor neuropathy occurs due to dying- back process of axonal degeneration.

Cognitive dysfunction in the form of deficits in concentration, memory defect. Behavioural disturbances in the form of anxiety, apathy, confusion, restlessness, labile emotion,lethargy, anorexia, insomnia, depression,irritability.

Metabolic complications such as hyperglycemia, glycosuria, presenting as hyperglycemic keto-acidosis, non-ketotic hyper glycemic acidosis.Parathion known to cause hemorrhagic pancreatitis which is fatal. Diazinon is also implicated in this scenario. Above all OPC is teratogenic as evidence by an incident in Hungarian village .Pregnant lady consumed fish contaminated by trichlorphos, 11 out of 15 live birth has congenital anomalies.Some reported anomalies are downs syndrome, ventricular septal defect, pulmonary atresia, anal atresia, stenosis of left bronchus..

In children it is also associated with certain non- hodgkins lymphoma such as burkitts lymphoma, lymphoblastic, large- cell, T-cell and B- cell lymphomas .Pediatric patients had predominately CNS depression and severe hypotonia, whereas muscarinic symptoms were infrequent.

DIAGNOSIS:

Depression of cholinesterase activity:

RBC cholinesterase is reliable than serum cholinesterase levels.Disadvantages includes wide variable normal level in various population.False low values are seen in pernicious anemia, hemoglobinopathy,anti-malarial treatment, sample collected in oxalate tube.High values are seen in reticulocytosis seen in anemia, haemorrhage, or else treated for anemia.

Depression of plasma cholinesterase activity:

Less than 50% reduction is less reliable indicator . More than 90% Reduction indicates increased mortality.As it is a liver protein, it is decreased in cirrhosis, malnutrition, chronic debilitating conditions, drugs such as succinyl choline, lignocaine, morphine, chloroquine..

p-nitrophenol test: metabolite of some OPC such as parathion excreted in urine.

This test also done in vomitus or gastric contents.Some studies shows that urine alkyl phosphates are more sensitive markers.

Thin layer chromatography(TLC):

Presence of OPC in vomitus,or gastric aspirate sample is determined by TLC .

Other ancillary investigations shows leucocytosis, high haematocrit, hyperglycemia, non-anion gap acidosis.ECG may show QTc prolongation or VPC, chest x ray shows evidence of aspiration pneumonitis , serum electrolytes, pancreatic amylase, CT-abdomen have to be taken if pancreatitis is suspected.

LEUCOCYTOSIS:

Increase in number of white blood cell due to acute inflammatory reaction.

It may be due to increased production from bone marrow , or increased release from marrow, or decreased margination or extravasation into tissues.Causes include any chronic infection/ inflammation will cause growth factor dependent leucocytosis.

Growth factor independent process is seen in myeloproliferative disorders.There are various types of leucocytosis such as neutrophilic , eosinophilic, basophilic, monocytic ,

lymphocytic leucocytosis.Morphology of neutrophils are classic as seen in sepsis, example toxic granulations., dohle bodies.

TREATMENT:

First and foremost step is identification of chemical and the attender is asked to bring the container or label as different OPC have different ageing and reactivation times. For example dimethyl OPC have early ageing so oximes should be initiated early. Diethyl OPC have delayed ageing so oximes have to be prolonged.

GOALS OF TREATMENT:

Airway, breathing, and circulation (ABCs): should be initiated first .Reduce absorption of the toxin (xenobiotic). Enhance elimination and neutralize toxin.Reduce absorption by decontamination of skin, eyes and hair, emetics, stomach wash, activated charcoal ,whole bowel irrigation. Skin decontamination– remove contaminated clothing and wash with soap and water.

Gastric Lavage:

Gastric lavage reduces absorption by 40% if done at 20 minutes and by 14% if performed at 60 minutes. Performed by repeated aspiration after instillation. Left lateral position delays absorption. Simplest, quickest and least expensive way is by means of funnel. Choice of fluid is tap water: 5–10 mL/kg.Preferably done on awake

patients.Presence of an ET tube does not preclude aspiration. No human studies in OPC shows benefits of gastric lavage.

Atropine: Atropine is a pure muscarinic antagonist that competes with ACh at the muscarinic receptor.

Atropinization Targets: Mandatory targets:

SBP greater than 100 mm Hg, Heart rate more than 110/minute, lung fields clear.

Other targets: Pupils dilated and Bowel sounds sluggish.

Targets on subsequent days: Day 2: HR greater than 100/minute

Day 3: HR greater than 90/minute ,Subsequent days: At least 80/minute.

Several recommendations > 20 mg atropine 0.02–0.08 mg/kg over 1 hour would take 4 hours to give 20 mg atropine to a 70 kg male. a minimum dose to prevent reflex bradycardia. Atropine may be redosed every 5 to 10 minutes.Disadvantage: not acting on nicotinic receptors. So not effective against neuro-muscular manifestations.

OXIMES:

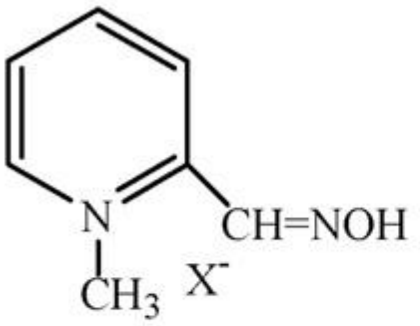
They are nucleophilic compounds compete with active site of bound acetylcholinesterase and reactivate them. The reactivation time varies depending upon ageing of various compounds.so it have to be initiated as early in dimethyl containing compounds and has to

been given for prolonged period in diethyl compound. Only available compound in united states is pralidoxime since 1950 .Now newer drugs such as obidoxime and trimedoxime are available.As per largest Oxime Trial treatment recommended is 2 g loading dose over 20 minutes,then 0.5 g/hour for maximum 7 days.Current evidence is insufficient and further studies have to be done to indicate whether oximes are harmful or beneficial. The WHO regimen (30 mg/kg pralidoxime chloride bolus followed by 8 mg/kg/hour infusion) is not in use in many centres reason for failure of oxime therapy is too early or delayed presentation, dosage used, type of OPC, toxicity of antidotes.

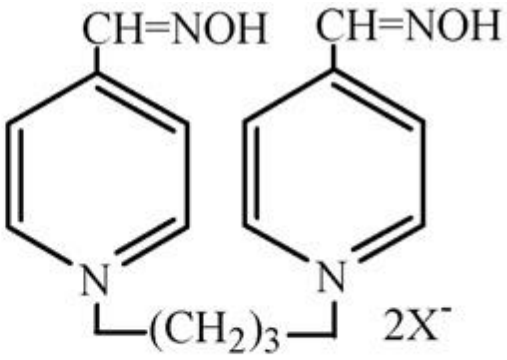
One study by Johnson et al was a comparison of bolus (1g)dosing versus Pralidoxime(12g) infusion. Mortality was higher in second group.

Another study by Cherian et al was a comparison of pralidoxime 12 g given over 3 days versus placebo..Mortality was higher in both groups.

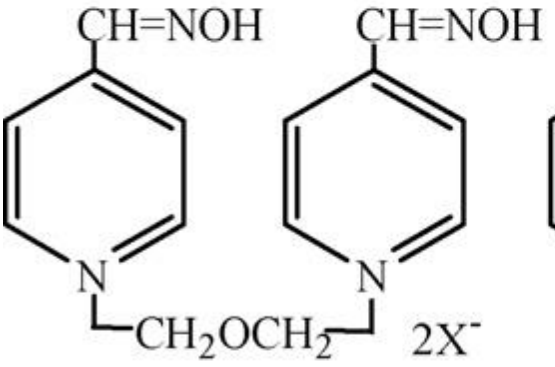
A recent study by Pawar et al compared continuous infusion of Pralidoxime, 1g/hour versus 1g fourth hourly. Both groups received 2g bolus dose.This reduces the need for intubation and minimize the dose of atropine. Former Group does better compared to later.



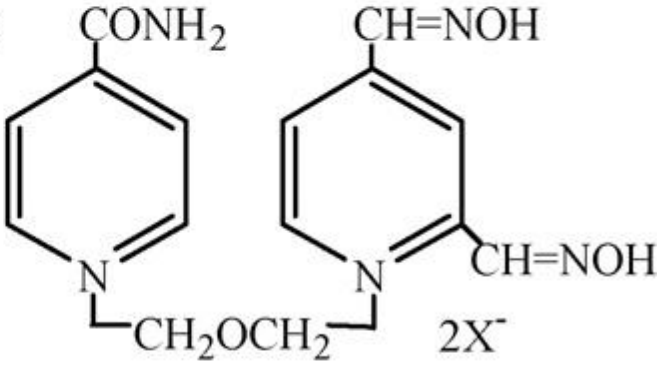
pralidoxime (PAM-2)



trimedoxime (TMB-4)



obidoxime, LüH-6
toxogonin



asoxime, HI-6

In OP poisoning it is hypothesized that butyrylcholinesterase present in FFP will sequester free unbound OPC present in blood and remove them from circulation .Based on various studies about bioscavenger therapy that fresh frozen plasma appears more harmful and prolongs the period of ventilatory support and intermediate syndrome. Also albumin as a bioscavenger therapy is also tried and of no proven benefit. This harmful effect is due release of sequestered OPC into circulation.

Early Enteral Feeding :

Early institution of enteral feeds may improve the outcome as it prevents entero-hepatic circulation. Early nutritional supplementation in OP poisoning may be harmful as it can lead to development of respiratory failure due to intermediate syndrome.

Clonidine is a centrally acting sympatholytic used as antihypertensive drug. It inhibits presynaptic release of acetylcholine, thereby decreasing the cholinergic symptoms. There is no benefit in OPC poisoning compared to side effects such as hypotension, bradycardia, rebound hypertension, sedation.

Charcoal: Activated charcoal has been widely used for absorbing poisons including pesticides, plant poisons, and drugs. The two methods of charcoal administration are single dose activated charcoal ,multiple dose activated charcoal. Charcoal adsorbs organophosphates and therefore may have a potential benefits in the treatment.

Gastric Lavage: Gastric lavage is most commonly used decontamination procedure across Asian countries.Organophosphates are absorbed easily through mucous membranes and gastric lavage may play a role in the early poisoning.

Alkalinisation by sodium bicarbonate have some benefits as the alkalinised products of some nerve agents soman are least toxic . $MgSO_4$ 4g iv improve outcomes in patients with

OP poisoning. Magnesium sulphate blocks calcium channels and thus reduces acetylcholine release. It reduces CNS overactivity due to N-methyl D-aspartate receptor activation.

Forced emesis (Ipecac) should not be performed because they may delay specific life-saving treatment.Adverse effects of ipecac may include bloody vomitus,loose stools, paralytic ileus, aspiration.

Role of benzodiazepines:

Used in OPC for control of agitation, sedation in ventilated patients, and for control of seizure . Diazepam, midazolam, lorazepam are commonly used drugs.They act by depressing all levels of activity, by increasing GABA activity,dose of lorazepam should not exceed 2mg/min,used for treating the status.Midazolam is water soluble takes longer time to act .It is also used for status especially when refractory.

Cathartics will reduce the transit time so that increase the passage of poison in GIT, so absorption will be reduced.

Gacyclidine is an anti-glutaminergic compound used in conjunction with anti-oxidants have some beneficial role in OPC as there is induction of reactive oxygen species and lipid peroxidation,increased thiobarbituric activity. Role of hemodialysis, hemofiltration, hemoperfusion in OPC is unclear.

COMPLICATIONS:

Most common mode of exposure is ingestion followed by dermal exposure and Inhalation.

Acute complication include, that is within 4 weeks seizure,hypotension,hyperglycemia, renal failure and diarrhoea.

Delayed complication include neurological deficit such as monoplegia involving lower limb or paraplegia with mild sensory involvement.

Mortality is mainly due to ARDS, arrhythmia and renal failure.

Iatrogenic complication is more common , example atropine overdose cause delirium, hyperthermia, diminished bowel activity, urinary retention, dryness of mouth as the famous saying, hot as hare, red as beet, dry as bone, etc. Treatment simply stop atropine until cholinergic symptoms supervenes.

Acidosis includes both metabolic, respiratory sometimes mixed component.Among them most common is metabolic component. Acidosis is due to tissue hypoxia, and treatment includes adequate oxygenation, ventilation and replacement of fluids.Mortality is mainly due to cardio vascular causes such as arrhythmias , followed by respiratory failure.So early arterial blood gas analysis and interpretation of complications is of prime significance.

Respiratory infection due to aspiration, ventilator associated pneumonia and its treatment with antibiotics is off little use.

Apart from muscaranic, nicotinic, central CNS symptoms patient sometimes develop extrapyramidal features such as tremors, rigidity, bradykinesia to akinesia. This is explained by a hypothesis, that the striatoniagral cholinergic neurons had diminished anticholinesterase activity, thus reducing cortical glutamate activity.It is supported by fact that treatment by amantadine reverses the symptoms probably due to anti-glutaminergic activity and due to NMDA antagonism. Other explanations such as hypoxic encephalopathy or dopaminergic changes have no evidence. Though the parkinsons features are transient it has to be diagnosed promptly to reduce complications.

Leucocytosis is a common finding. It suggest the prognosis such that normal count on admission have less complications. It has to be serially monitored. Increased count despite treatment succumbs to complication such as respiratory failure, chest infection, urinary tract infection.

BIOCHEMICAL CHANGES:

Respiratory changes: Loss of respiratory drive leads to bradypnoea or apnoea.Some studies shows that there is no evidence of respiratory muscle paralysis, as diaphragm is intact.

Hepatological changes: both activation and de-toxification occurs in liver.

Some histological changes occurs are congestion, centri-lobular necrosis, fatty

changes and sinusoidal dilatation.

Cardiovascular changes: Myocardial necrosis as evidenced by increase in creatinine phosphokinase and lactate dehydrogenase. Other changes include sinus tachycardia, sinus bradycardia, hypotension, hypertension. ECG changes include ST elevation, QTc prolongation, low amplitude T wave,ventricular premature complexes , various degrees of heart block as evidenced by prolonged PR interval.

Neurological disorders:

Cognitive dysfunction and defective in working memory are usually seen as chronic complication.The symptoms even persists for more than 6months.Other syndrome include parkinsonism, pseudobulbar features sometimes cerebellar features.

Four types of neurological manifestations:

- cholinergic crisis
- intermediate syndrome
- OPIDN(organophosphate induced delayed polyneuropathy)
- COPIND(chronic organophosphate induced neuropsychiatric disorder)

CHOLINERGIC SYNDROME:

It is the first phase of OPC poison.Symptoms due to action of excess of acetyl choline on nicotinic or muscarinic receptors.Most severe manifestation is respiratory failure.Also called as type 1 paralysis.

INTERMEDIATE SYNDROME:

First coined by senanayakae from srilanka in 1987. Described as type2 paralysis by wadia in 1974. Called intermediate as it occurs after initial cholinergic phase but before late polyneuropathy. Mechanism remains still unclear.Usually initial manifestation is weakness of neck flexors followed by proximal limb weakness , respiratory paralysis, sometimes cranial nerve palsy. It occurs after 24 to 96 hours after ingestion.Order of recovery is cranial nerve followed by limb and respiratory muscles.As per Gadoth and Fisher views, its due to action on nicotinic Receptors. As per senanayake its due to downregulation of acetylcholine receptors. Deep tendon reflexes are depressed, sometimes pyramidal tract is involved. Decremental response at low frequency stimulation as evidenced by nerve conduction studies.Compounds implicated are monocrotophos, dimethoate, methyl Parathion Serum acetyl cholinesterase is grossly reduced. All these patients require ventilator support. Incidence is around 29%. Time of recovery is between 3 to 12 days.

OPIDN:

Produced by compounds having weak anti-cholinesterase activity.Example,Triorthocresyl phosphate. It occurs after 7 to 21 days following exposure.Symptoms manifest initially as parasthesias and leg pain, then followed by leg weakness,manifest as footdrop. Then weakness of small muscles of hand later involves the truncal muscles. Cranial nerves and

autonomic system not involved.Deep tendon reflexes are absent,ataxia can also occur, for such cases prognosis is guarded.Its due to aging of neuropathy target esterase.

COPIND:

These effects include drowsiness,confusion, lethargy, anxiety, emotional lability,depression, fatigue and irritability. This is due to hypoxic sequelae attributed to respiratory failure and cardiac arrhythmias that occurs during cholinergic phase.

Extra-pyramidal features too occurs.

Hormonal disorders:

Hormonal imbalance usually involves sex hormones .Maternal exposure may lead to foetal death, intrauterine growth retardation ,and infertility in both sexes.

Other effects: on oesophago-gastroscopy, edema and bleed is seen throughout the esophagus.

As per study conducted by Ontario college there is risk of renal carcinoma .Due to chronic exposure to pesticides among children can lead to renal failure.Studies shows that it's a state of oxidative stress , as evidenced by enhanced lipid peroxidation and decreased level of glutathione.

LABORATORY FEATURES as observed by HAYES et al

As per his observation , depleted anticholinesterase is seen in 97%,

Polymorphonuclear leucocytosis in 46%, Proteinuria in 18%, glycosuria- 14%

hyperglycemia in 7 % and abnormal ECG in 5%..

FUTURE DRUGS:

Huperzine-A:(HupA)

Reversible inhibitor of acetylcholinesterase. Oral formulation is derived from extracts of huperzia serrata.Used for treating memory deficits in alzheimers disease, vascular dementia.Now is in trial.Minimal cholinergic side effects and higher oral bio-availability and prolonged action.

ZT-1 similar profile compared to HupA. Both can cross the blood brain barrier.

Butane - 2, 3-dionethiosemicarbazone is an oxime with antioxidant properties

Its action is to nullify the different forms of free radicals such as hydroxyl ,nitric oxide radicals and inhibit lipid peroxidation.

Phosphotriesterases (PTEs):

The main enzymatic systems involved in the detoxification of OPC are phosphotriesterases, carboxylesterases, and glutathione-S-transferases.Most commonly studied PTESs are paroxonases..

VENTILATORY MANAGEMENT IN OPC:

According to recent guidelines:

Direct indices: arterial oxygen tension < 50 mmHg in room air

Arterial CO_2 tension > 50 mmHg in the absence of metabolic alkalosis.

Derived indices:

PaO2/FiO2 < 250 mmHg

PAaO2 (pulmonary arterial-alveolar O2 gradient) > 350 mmHg

Vd/Vt >0.6

Clinical – respiratory rate (RR) > 35 breaths/min

Mechanical indices:

Tidal volume 5ml/kg

Vital capacity 15 ml/kg

Maximum respiratory force < 25 cm of H2O

BENEFITS of OPC:

Apart from various adverse effects there are certain benefits as a pesticide that can kill pests, rodents, that poses serious problem in community so that they can reduce the incidence of various vector-borne diseases,asthma and allergic diseases,microbial contamination and avian flu,anthrax, prion disease,etc.

PREVENTION of OPC:

- Adequate ventilation when applying pesticides in home.
- Don’t use outdoor pesticides in indoor.
- Follow the labelled instructions and safety warnings.
- Use ready-made products whenever possible.

- Protect foodstuffs and water supplies from the vicinity of pesticide.
- Wash before consumption.
- Container should be discarded safely.
- Use gloves and protective jackets while applying pesticides.
- Before using pesticides wash your hands with soap water.
- Pesticides and poisons should be kept away from the children.
- Adequate education about various hazards of poisons to children
- Pouring pesticides into river, dam , toilet drain leads to contamination of water resources.

Based on various randomised control trials certain therapies are likely to be beneficial and proven ,unknown effectiveness ,unlikely to be beneficial, sometimes harmful.

Of proven benefit

Atropine, Glycopyrrolate,benzodiazepines to control organophosphorus-induced seizures and removing clothes contaminated with OP poison.

Effect not known

Activated charcoal ,Alpha2 agonists ,cholinesterase replacement therapy Extracorporeal clearance ,Gastric lavage ,Magnesium sulphate,N-methyl-D-aspartate receptor antagonists ,Organophosphorus hydrolases ,Oximes and Sodium bicarbonate.

Not beneficial---Cathartics

ineffective or harmful - ipecac

Merits and demerits of various intervention :

ATROPINE: case series shows that atropine reversed the early muscarinic effects of acute OP poisoning.

Harm: confusion and tachycardia ,ventricular tachycardias.

OXIMES:There are various regimen followed in different centres.Accordingly mortality, need for ventilation, incidence of intermediate syndrome varies.Also it reduces the dose of atropine needed.

Harm: Adverse effects of oximes include hypertension, cardiac arrhythmias, headache, visual disturbances, epigastric pain. Adverse effects with pralidoxime due to rapid administration or dose >30mg/kg/bolus.Obidoxime known to produce hepatitis at the dose of 8mg/kg / bolus.

General principles in management of poisoning:

- Prevention of contamination of the rescuing people
- If the victim is unconscious or gasping for respiration, commence Resuscitation followed by supportive care
- Decontamination of the patient.
- To remove the poison from the body by various techniques

- Specific management of particular poisons by antidotes.
- Treatment of complications of the poison.
- Call for help and ambulance as soon as possible.

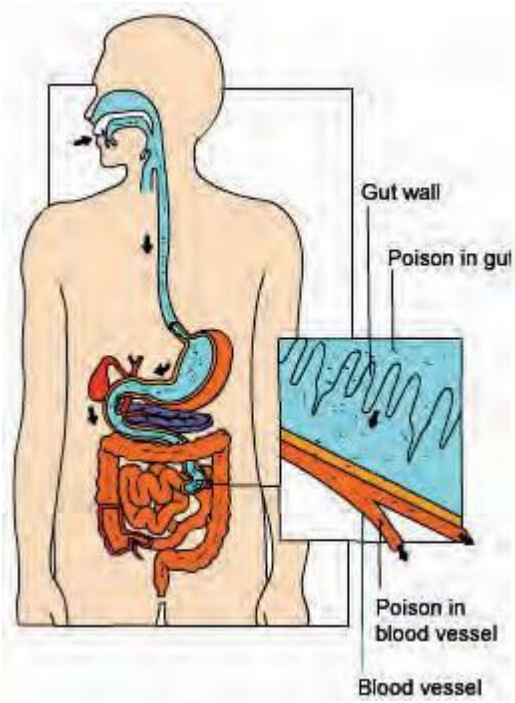
Prevention of poisoning of the rescuer

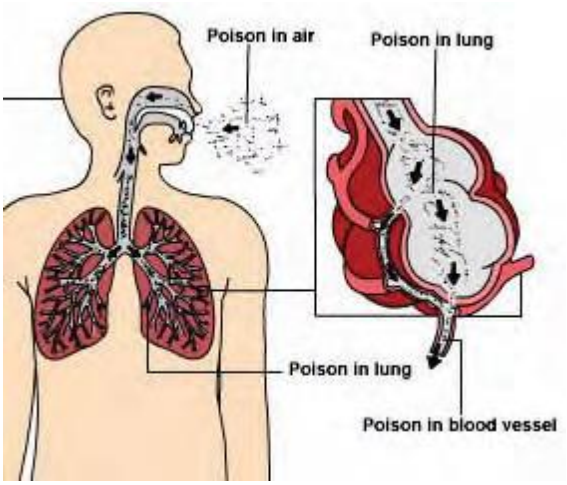
- During first aid and subsequent treatment, the container should be identified to minimise further exposure.
- WHO colour code on container can also give clue.
- Monocrotophos, Phorate and Methomyl are class I toxic pesticides available in local market.
- Rescuer need to wear personal protective equipment (PPE) including gloves and jackets during decontamination.

- **Decontamination**

  If the poison is ingested wash their mouth with soap. Don't use emetics..

  If the poison is inhaled immediately get the person to fresh air.Avoid breathing fumes.



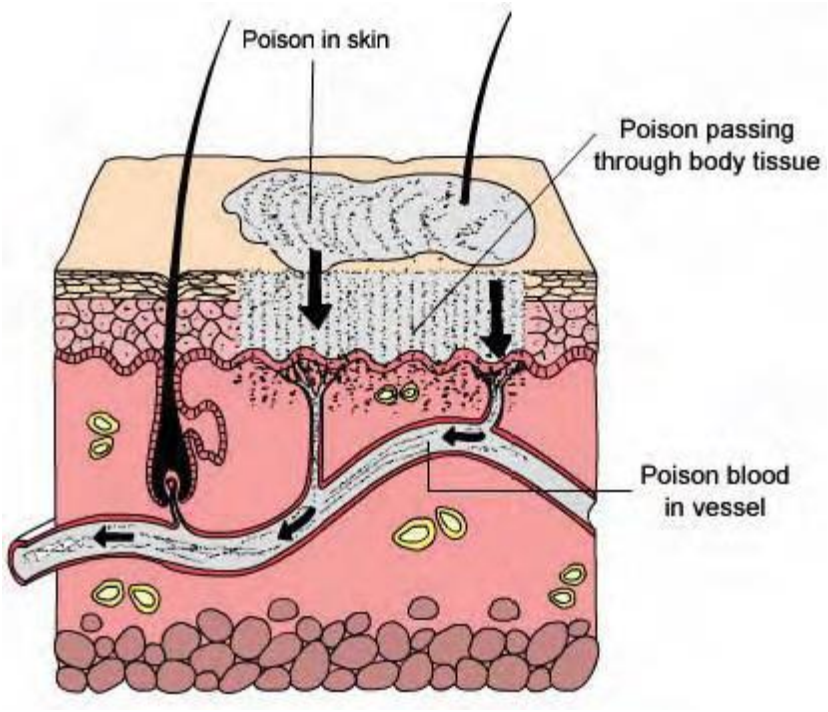


If the poison contacts with eye warm the eye with saline or cold water.

If the poison contacts with skin remove contaminated clothing

Flood skin with running cold water.

Wash gently with soap and water and rinse well.



Resuscitation and supportive care

A self-inflating bag-valve-mask apparatus is the safest way to provide ventilation for the BLS rescuer

Specific Management of particular poison

ANTIDOTE:

An antidote is a substance which can counteract a form of poisoning.

The term derived from greek word antididonai, given against.

Therapeutic substance used to counteract the toxic action of specified xenobiotic.

ROLE OF ANTIDOTES:

Neutralise the toxin of its effects

- Save the patient from death
- Shorten the hospital stay
- Reduce the burden on health services
- Especially important in developing countries where adequate facilities are not available in primary care.

Unavailability of antidotes or delayed use could result in catastrophic sequences.

ANTIDOTES SHOULD BE AVAILABLE IN EMERGENCY:

Activated charcoal:

Activated charcoal is a fine , black odourless powder made from burning wood or coconut shell followed by treatment with activating agent like steam by virtue of its large surface area it adsorbs many drugs and toxins.Useful for drug overdose whose half-life is long.

Atropine:

Used in OPC, carbamate, and nerve agent poisoning.It is a parasympatholytic agent that competitively blocks action of acetylcholine at muscarinic receptors.

Cyanide antidote kit(CAK):

amyl nitrite, sodium nitrite and sodium thiosulphate. Useful in cyanide poisoning.Hydroxycobalamin is packed to allow field use or pre-hospital use.

methylene blue:

Used in methemoglobinemia with hypoxemia, dysnoea, confusion and chest pain or methhemoglobin level greater than 30%. It is a thiazine dye that increases the conversion of methhemoglobin to haemoglobin.

Oximes:

Pralidoxime is the only available oxime in india.It is a antidote for OPC poison. Also used in nerve agent agent exposure.

Ethanol and fomepizole:

Antidote for suspected methanol or ethylene glycol poisoning.

Chelating agents:

Capable of forming coordinate bonds with metals and make it water soluble resulting in high renal excretion.

Example: BAL:(british anti-lewisite) used in arsenic, mercury, gold, lead poisoning.

CaEDTA: used in lead poisoning.

D-penicillamine: chelates lead,mercury and copper.

DMSA: chelates lead, mercury arsenic.

RECOMMENDATIONS:

- New legislation have been adopted by ministry of health and family welfare regarding stocking of antidotes.
- Co-ordination of PHC.CHC, tertiary hospitals regarding quantity of antidote and where to direct the poisoned.
- Antidote bank in each state
- Life saving antidotes should be given to all major chemical industries
- Establishing a toxicology response centre- emerging need.

Carry home messages in OPC management:

We recommend incremental dose administration of atropine as the standard of care. The role of glycopyrrolate alone or in combination with atropine is not clear.Overall null effect or potential harm with oximes was found on meta-analysis of trials. The largest oxime study tends to harm. Fresh frozen plasma appeared to be more harmful than beneficial. Early institution of enteral feeds may be associated with improved outcomes in the critically ill as it prevents enterohepatic circulation . An optimum dose of clonidine with clonidine bolus injection (0.15–0.30 mg) followed by an infusion at the rate of 0.5 mg/24 hours appears to be clinically acceptable in OP poisoning. Activated charcoal use in acute OP poisoning: No evidence of harm or benefit. Gastric lavage in OP poisoning shows no evidence of harm or benefit. However, this

being an easily performed and cheap intervention could be used as an adjunct measure.Blood alkalinization with high dose $NaHCO_3$ in OP poisoning was shown to be useful. External decontamination: washing with soap and water can reduce further absorption of the poison into the system

Intravenous $MgSO_4$ (4 g) given in the first day after admission has been shown to decrease hospitalization period and improve outcomes in patients with OP poisoning. Forced emesis (Ipecac) should not be performed on patients with OP poisoning.Benzodiazepines are widely used in OP poisoning to control agitation, provide sedation in ventilated patients and control of seizures

Cathartics can reduce the transit time and reduces the absorption of poison

Gacyclidine: Antioxidants are useful adjuvant therapies in OP.

Prognosis

In severe poisoning, death usually occurs within first day if left untreated.

With nerve-agent poisoning, death may occur within minutes if untreated.

Even with adequate respiratory support and specific treatment with atropine and oximes, the mortality rate is still climbing in severe poisoning.

A delay in treatment can lead to late neurologic sequelae. Most patients with mild poison can recover completely .

MATERIALS AND METHODS

study design:

This is a cross- sectional study.

Place of study:

Study was carried out in the department of medicine , intensive medical care unit Tirunelveli medical college hospital.

Study population:

All patients admitted in IMCU with alleged history of consumption of OPC Poisoning.

Inclusion criteria:

All patients (both males and females) admitted in the IMCU with consumption of organophosphorus compound.

Exclusion criteria:

Known diabetic,known case of chronic pancreatitis ,previous history of cholelithiasis,previous history of pancreatic procedures,alcoholics,dyslipidemia drug induced pancreatitis.

Study method:

This study was approved by ethical committee of our institute. Patients were selected for the study as per inclusion criteria and exclusion criteria mentioned above. Detailed history regarding diabetes mellitus,alcoholism, drug abuse, pancreatic procedures, any other pancreatic disorder,gall stone disease have been enquired. Vitals were noted. Basic investigations such as total leucocyte count, haematocrit and random blood sugar, were done.Urine analysis was done. Pancreatic enzymes such as amylase and lipase were taken into account. Radiodiagnostic studies of abdomen were done.

Diagnosis:

Was made by history of consumption of OPC poisoning, and clinical features suggestive of OPC and identification of container.

Leucocytosis:

Increase in number of WBC for any type of inflammatory reaction. Here we observe neutrophilic leucocytosis more than 10,000 caused by pancreatic inflammation or necrosis.

random blood sugar:

hyperglycemia (>200 mg/l) is because either to stress hyperglycemia

or hyperinsulinemia or endocrine insufficiency of pancreas.

Haematocrit: >45 suggest haemoconcentration caused by intravascular volume loss and

<35 suggest either blood loss due to Pancreatic necrosis.

Serum amylase:

Considered elevated if > 190 IU/dl , excluding other causes of hyperamylasemia

Serum lipase:

Considered elevated if > 55 IU/dl , and it is more specific for pancreatic

Inflammation..

All the data are collected meticulously and entered into proforma and master

chart was prepared.

RESULTS AND OBSERVATION

Statistical method:

Data were analysed using computer based software by chi-square test.

p-value < 0.05 was considered as statistically significant.

Table 5.1:AGE DISTRIBUTION IN STUDY POPULATION:

AGE	< 190	> 190
< 30	30	2
31 TO 40	39	2
40 TO 50	17	2
> 50	8	0
total	94	6

p value 0.929 - not significant

Inference(Table 5.1):

consumption of OPC is more in middle aged people.That is between 30 to 40

years of age.

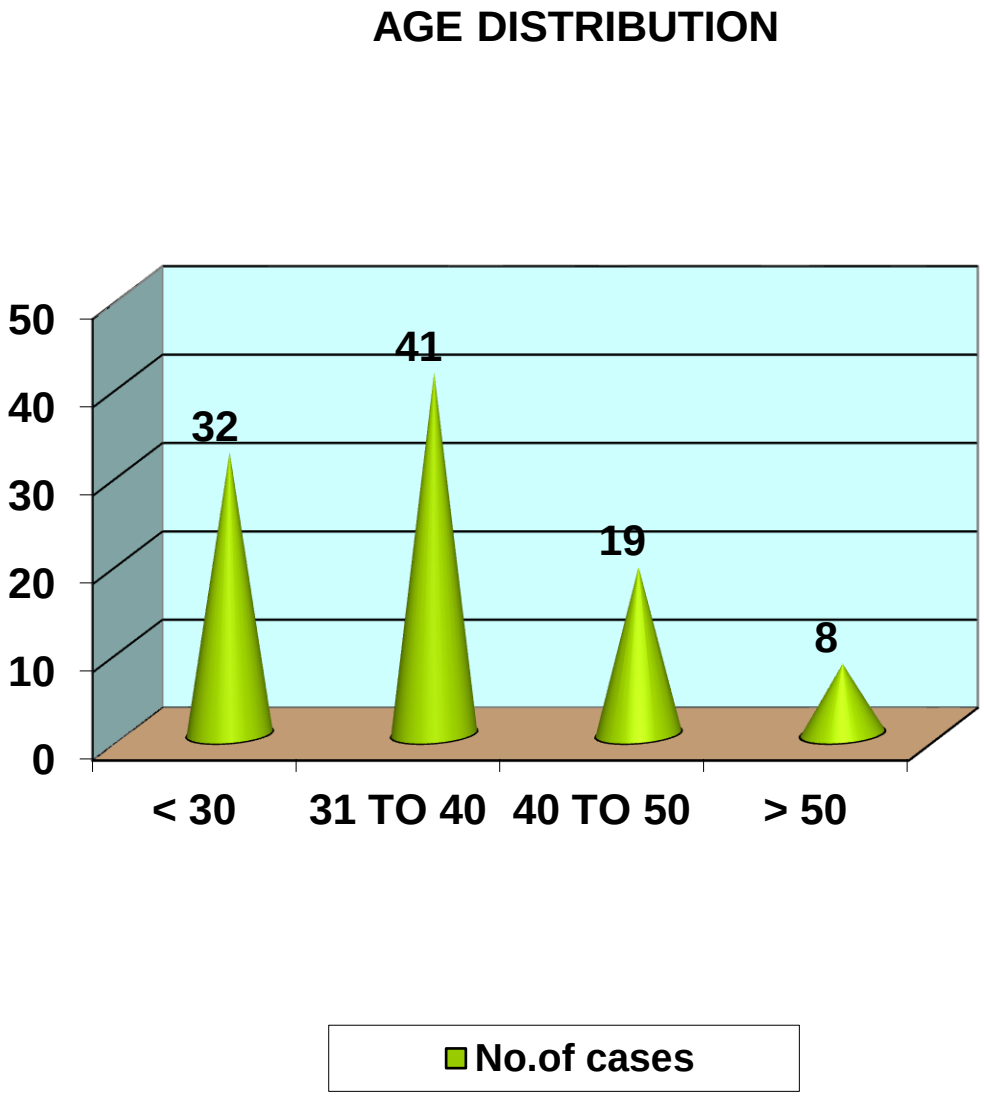


Figure 5.1: age distribution in study population

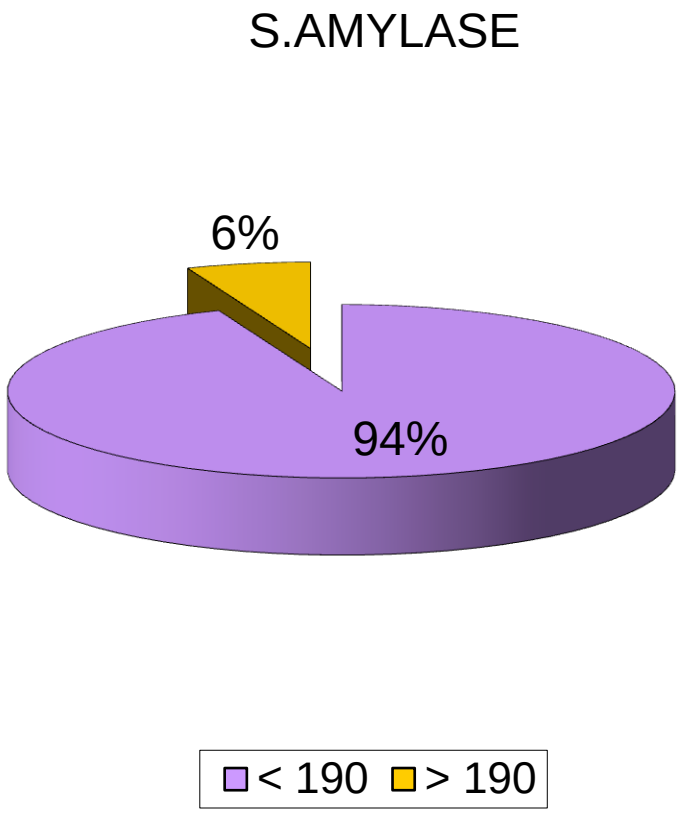


Figure 5.2: prevalence of hyperamylasemia in study population

Table 5.2

S.AMYLASE			
< 190	94		
> 190	6	<0.001	Significant
total	100		

Inference: OP poison associated with increase in pancreatic enzyme, amylase in 6% of study population

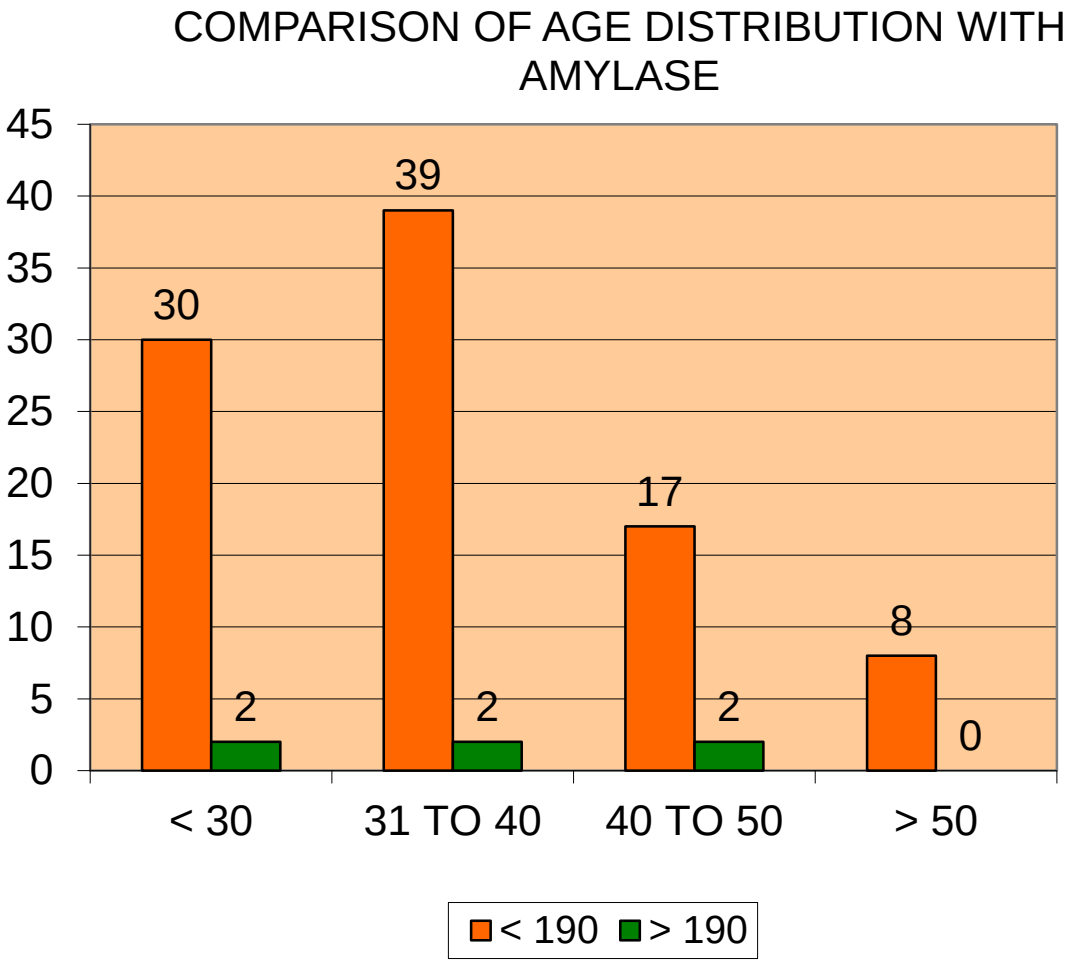


Figure 5.3: amylase levels in various age in study population

Inference:

the incidence of hyper amylasemia is equally distributed between various age groups so it is not statistically significant.

Table 5.3: age distribution among study population

AGE	< 190	> 190	
< 30	30	2	
31 TO 40	39	2	
40 TO 50	17	2	
> 50	8	0	0.929 Not significant
total	94	6	

Inference:

Incidence of OPC poisoning is equally distributed among various age Groups.

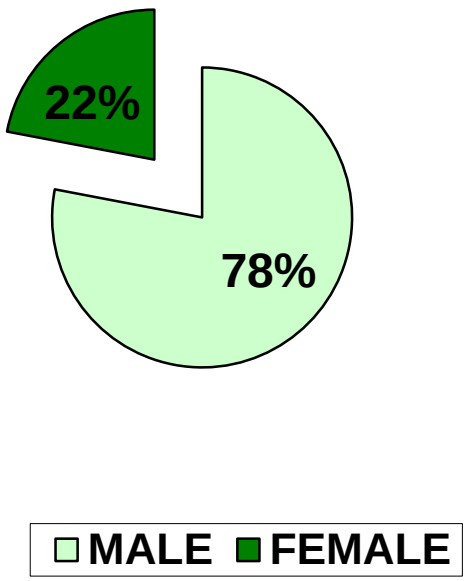
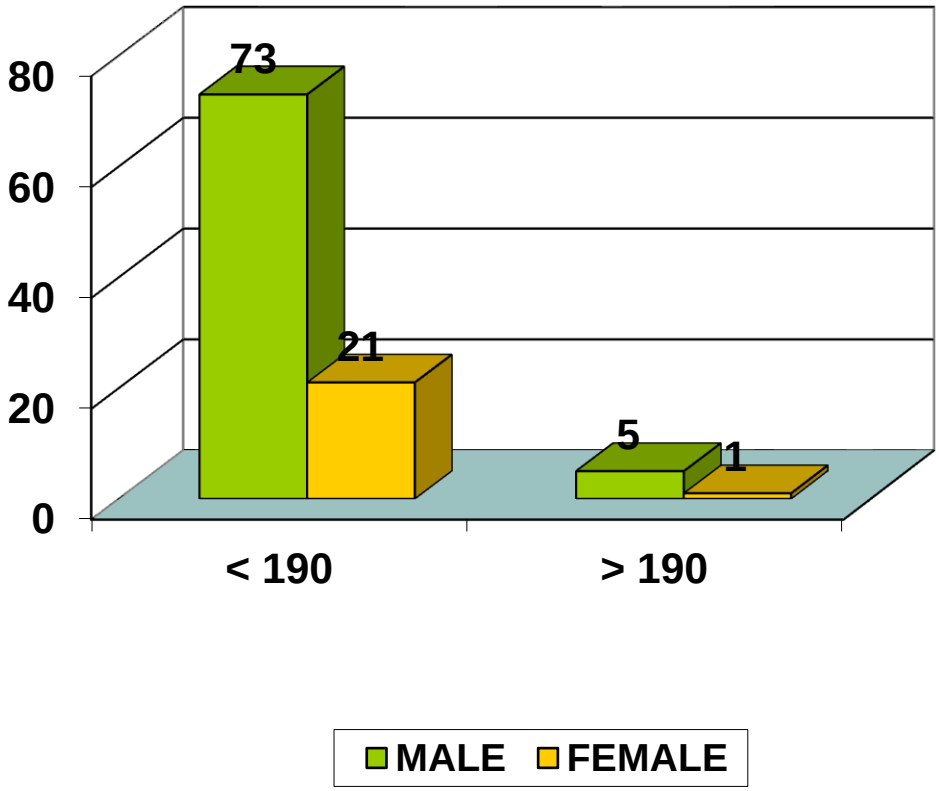


Figure 5.4: sex distribution in study population

Table 5.3

SEX	< 190	> 190	
MALE	73	5	
FEMALE	21	1	0.841 Not significant
total	94	6	

AMYLASE VS SEX



Inference:

OP poisoning is more common among male sex.The prevalence of hyperamylasemia is equal among, male and female sex..

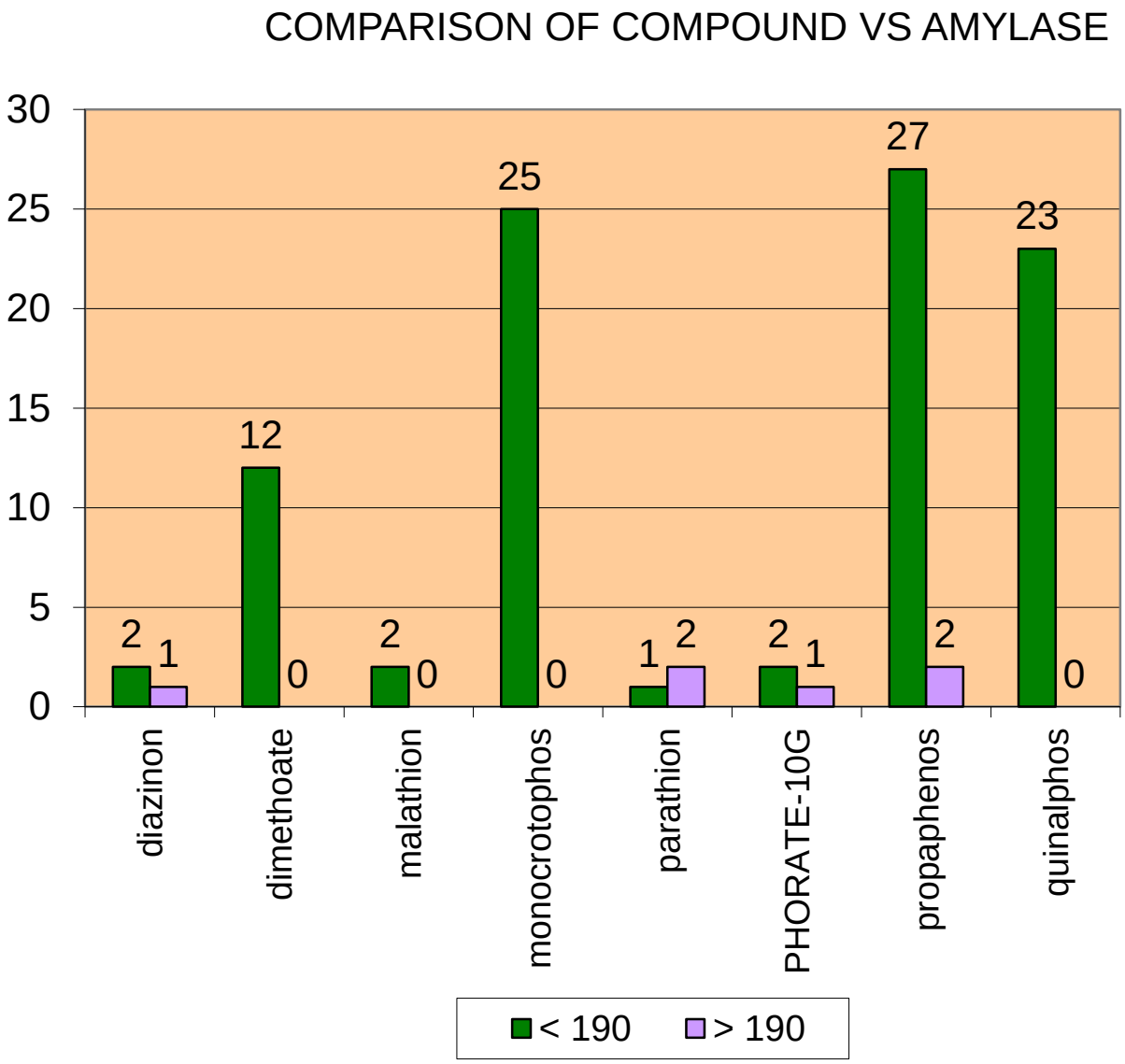


Figure 5.6: association of amylase with various OP compounds

Table 5.4: association of amylase with various OP compounds

COMPOUND	< 190	> 190	
diazinon	2	1	
dimethoate	12	0	
malathion	2	0	
monocrotophos	25	0	0.464 Not significant
parathion	1	2	
PHORATE-10G	2	1	
propaphenos	27	2	
quinalphos	23	0	
total	94	6	

Inference:

There is no significant relation between various compounds and amylase levels.

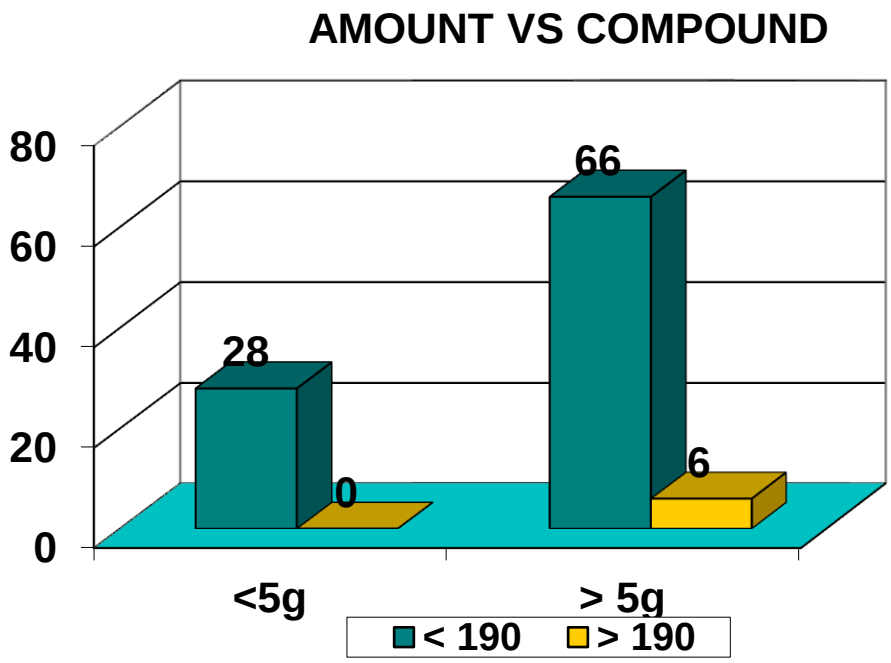


Figure: 5.7: association of amount and amylase levels

Table 5.6

AMOUNT	< 190	> 190	
<5g	28	0	0.411 Not significant
> 5g	66	6	
total	94	6	

Inference: prevalence of hyperamylasemia is seen only in person who consumed more than 5grams

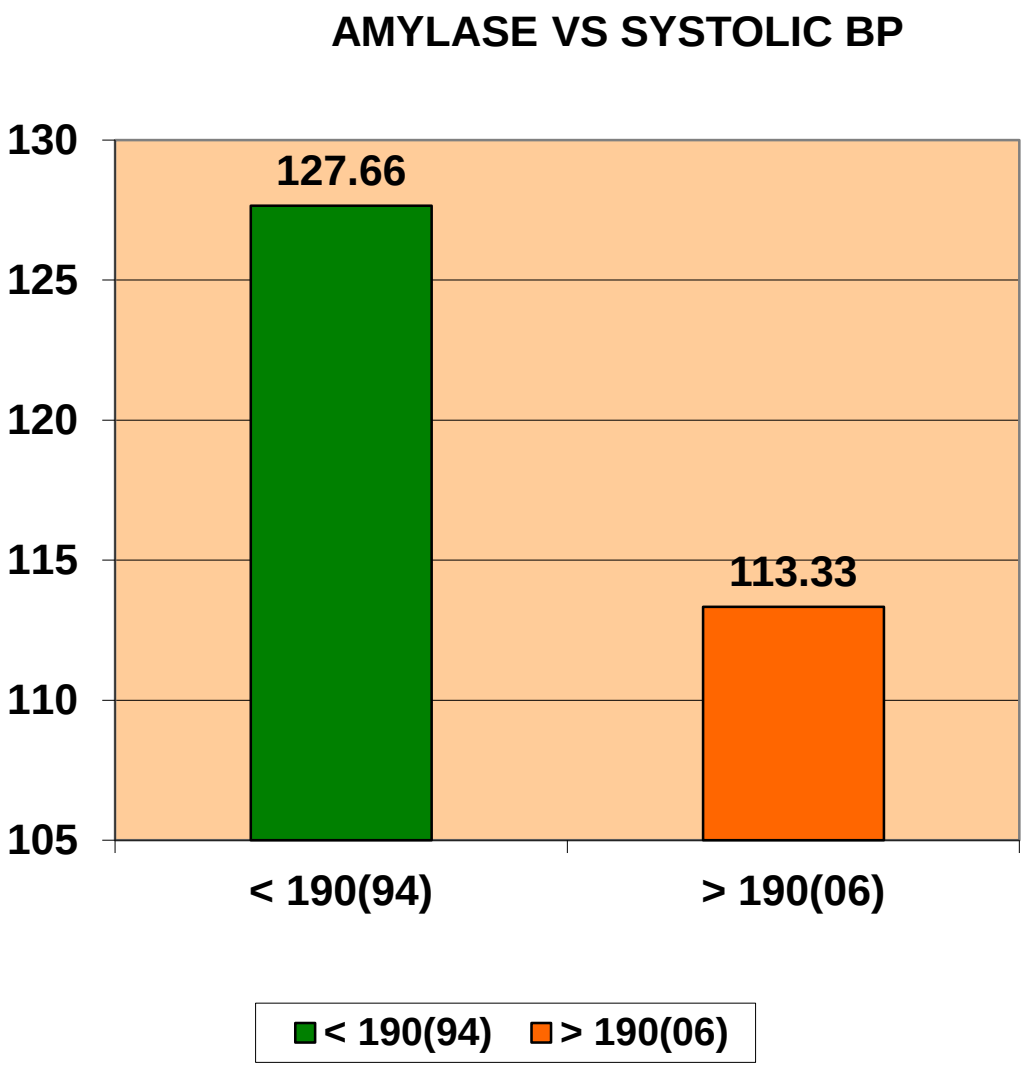


Figure 5.8 association of amylase and systolic BP

Table 5.7: association of amylase and systolic BP

	Systolic BP mmHg			
S.AMYLASE	mean	STD	P' Value	
< 190(94)	127.66	22.83	0.157	Not significant
> 190(06)	113.33	38.3		

Inference:

Elevation of amylase is associated with mild decrease in systolic blood pressure, but is not significant.

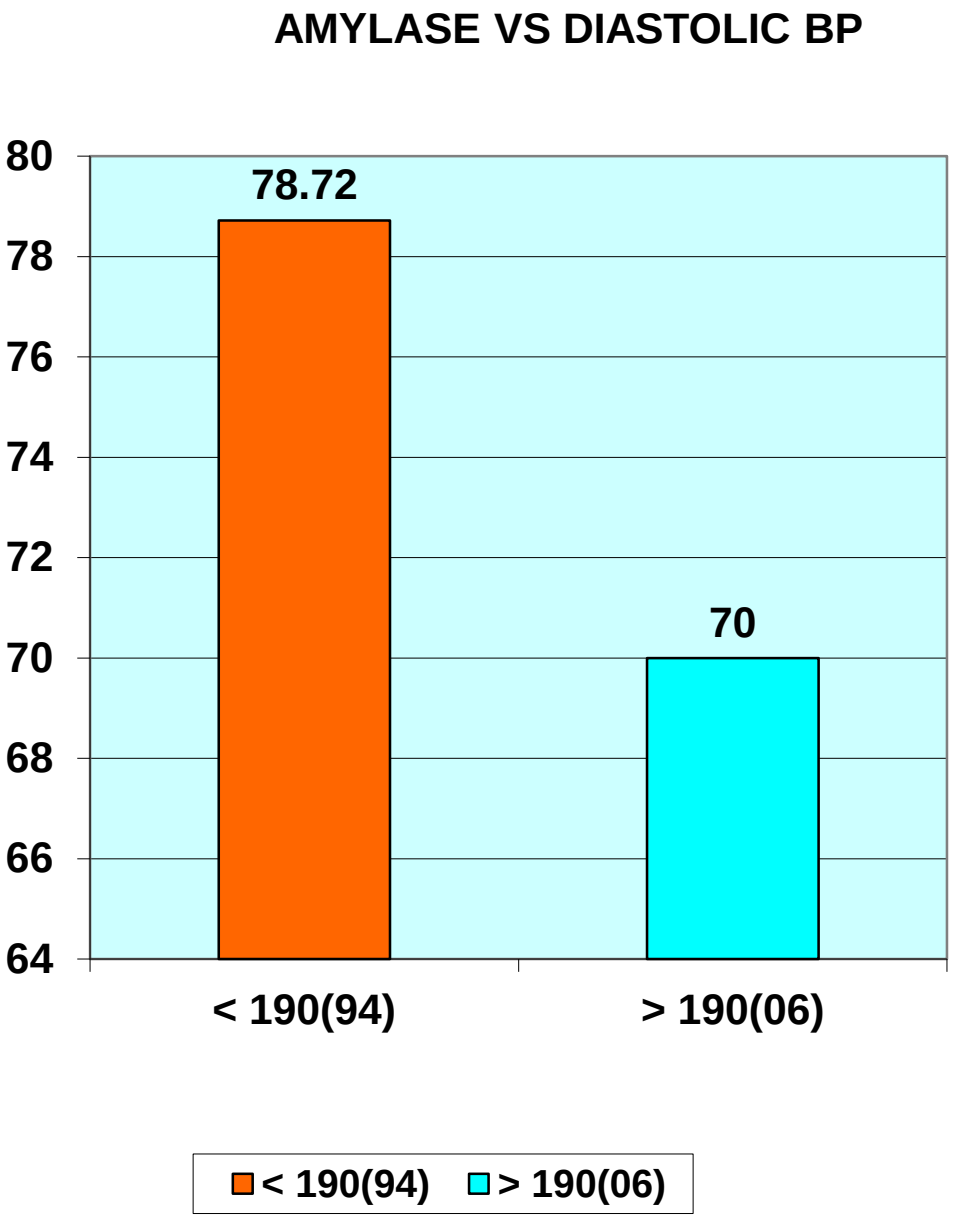


Figure 5.9: association of amylase and diastolic BP

Table 5.8: association of amylase with diastolic BP

	BP mmHg diastolic			
S.AMYLASE	mean	STD	P' Value	
< 190(94)	78.72	10.1	0.078	Not significant
> 190(06)	70	20		

Inference:

There is mild decrease in diastolic blood pressure in patients with Hyperamylasemia..

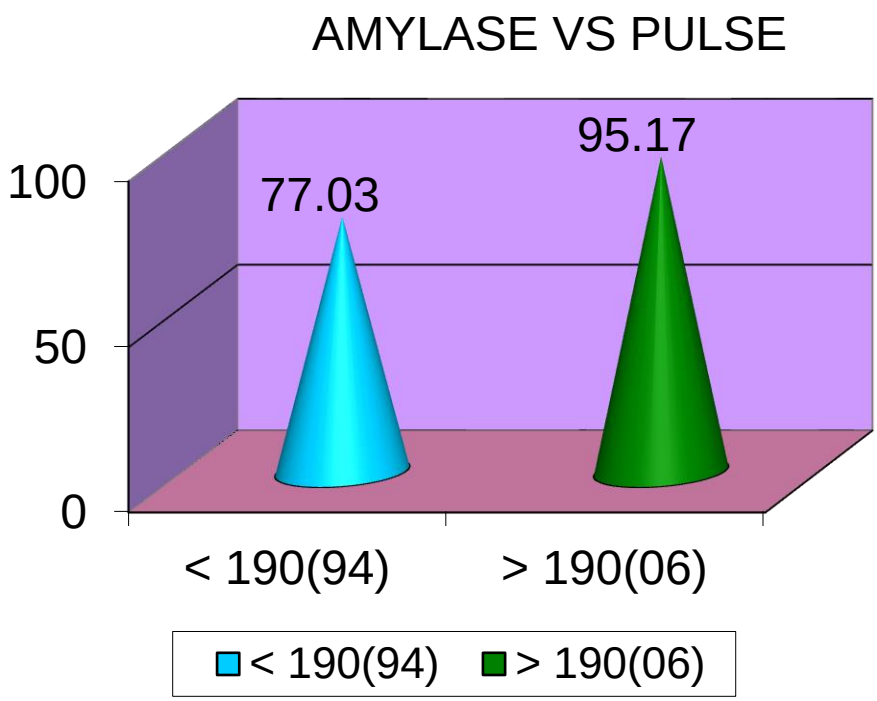


Figure 5.10.. association of amylase with pulse rate

Table 5.10

	PULSE/min			
S.AMYLASE	mean	SD	P' Value	
< 190(94)	77.03	19.23	0.034	Significant
> 190(06)	95.17	32.1		

Inference: observation of increased pulse rate in hyperamylasemia was significant.

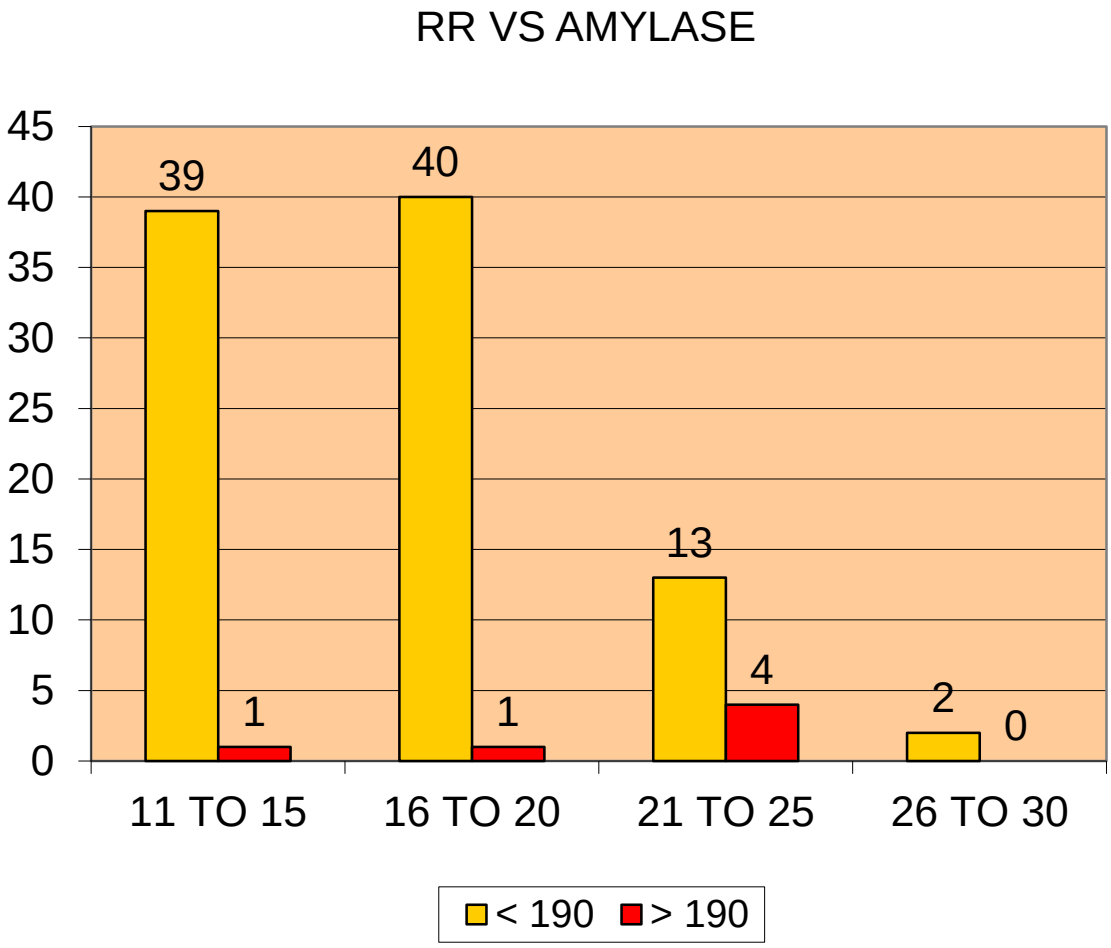


Figure 5.11:association of amylase with respiratory rate

Table .5.10: association of amylase and respiratory rate

RR/min	< 190	> 190				
11 TO 15	39	1		RR		
16 TO 20	40	1	S.AMYLASE	mean	STD	P' Value
21 TO 25	13	4	< 190(94)	16.81	3.59	0.027
26 TO 30	2	0	> 190(06)	20.33	5.13	
total	94	6				

Inference:

Increased respiratory rate is associated with hyperamylasemia was considered significant..

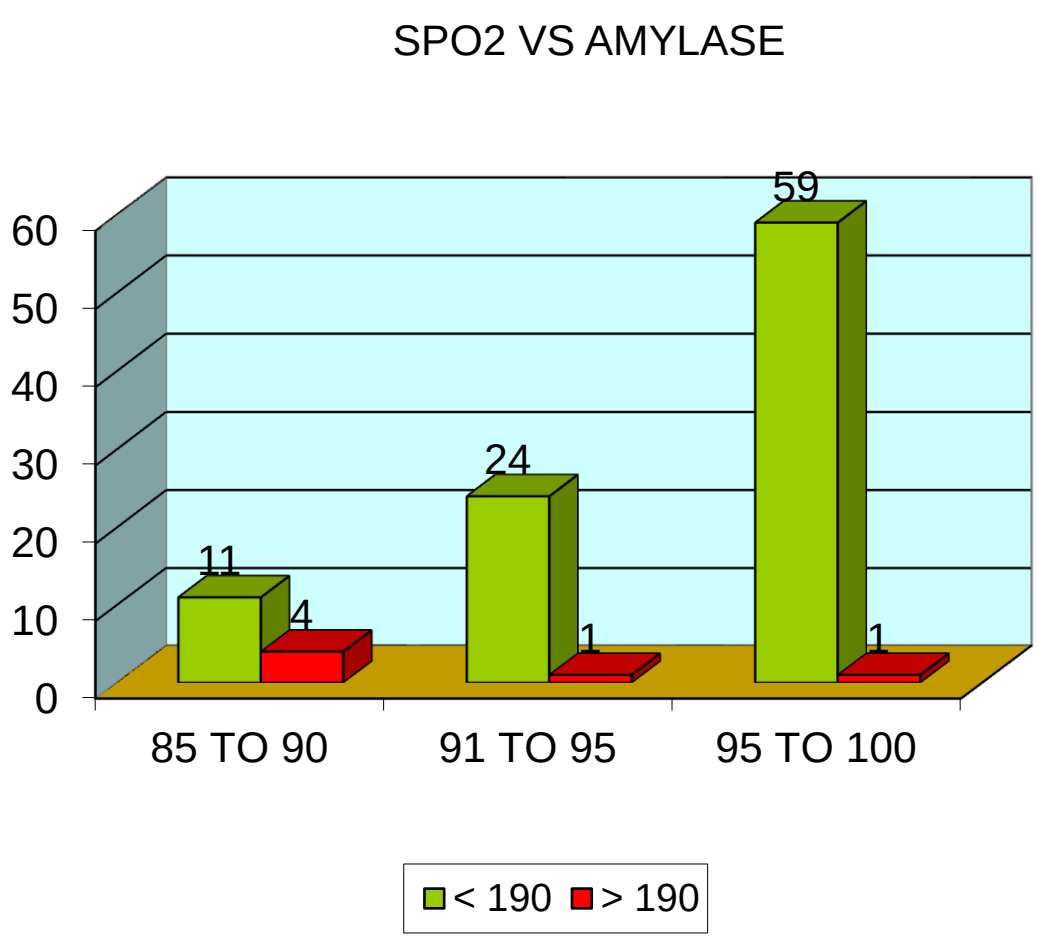


Figure: 5.12: association of SPO2 with amylase

SPO2 %	< 190	> 190				
85 TO 90	11	4		SPO2		
91 TO 95	24	1	S.AMYLASE	mean	STD	P' Value
95 TO 100	59	1	< 190(94)	95.22	2.75	< 0.001
total	94	6	> 190(06)	90.83	4.02	

Table: 5.11:association of amylase with SPO2

Inference:

Increased prevalence of decreased oxygen saturation in patients with hyperamylasemia..

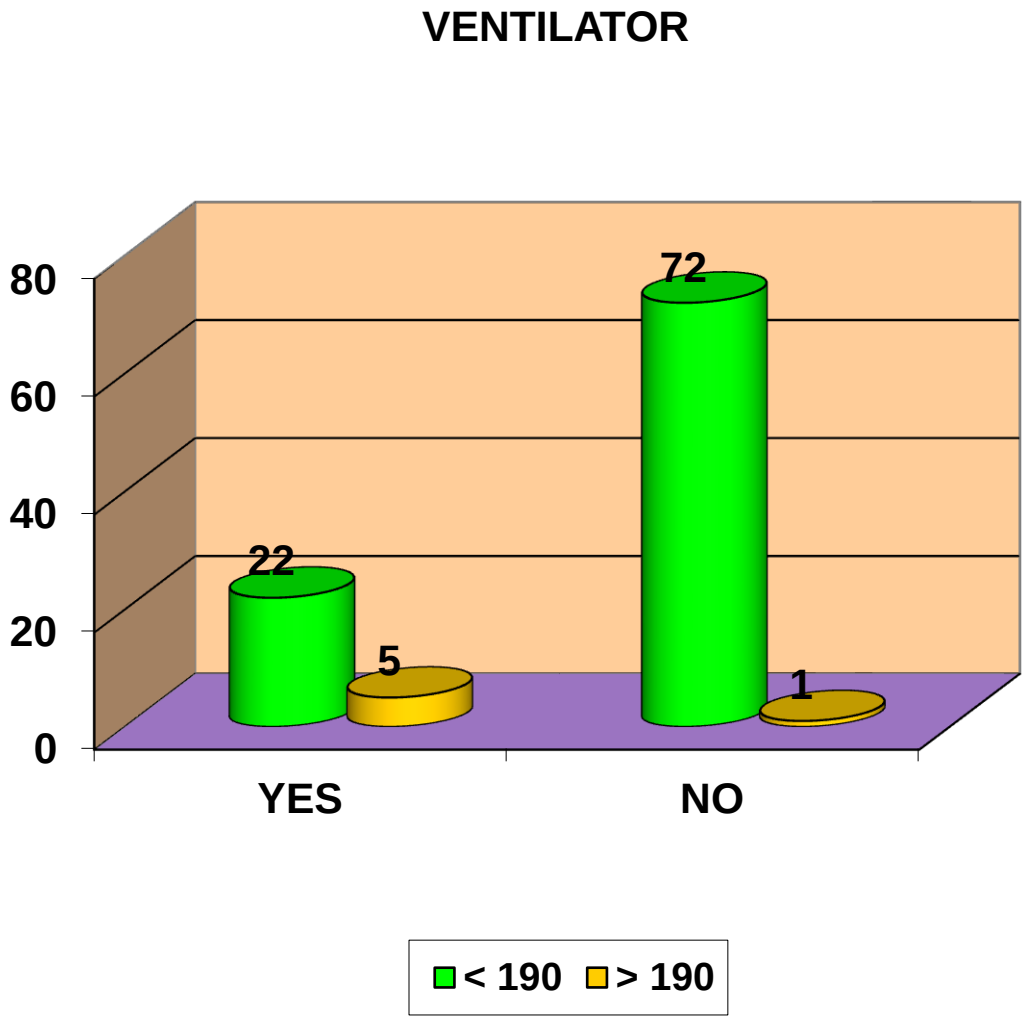


Figure 5.13: association between amylase and ventilatory support

ventilator	< 190	> 190	
YES	22	5	
NO	72	1	0.096 Significant
total	94	6	

Table 5.12: association of amylase and ventilatory support

Inference:

Increased amylase levels are correlated with increased need for ventilator Support.

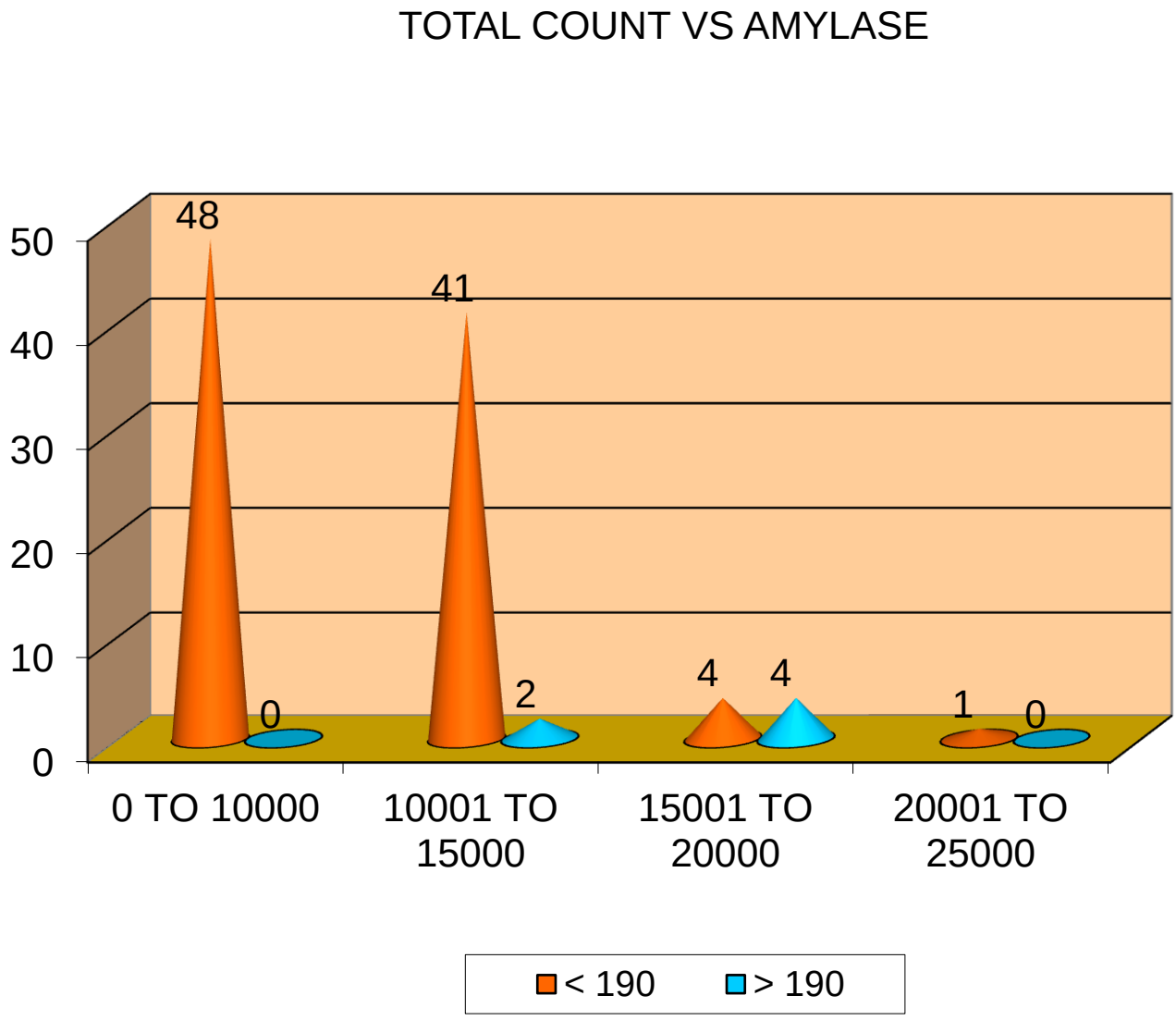


Figure 5.14: association between leucocyte count with amylase

TC	< 190	> 190	
0 TO 10000	48	0	
10001 TO 15000	41	2	
15001 TO 20000	4	4	0.198 Not significant
20001 TO 25000	1	0	
total	94	6	

Table 5.13: association of leucocyte count with amylase

Inference:

Leucocytosis is associated well with OP poisoning.But doesnot correlate well with increased amylase level..

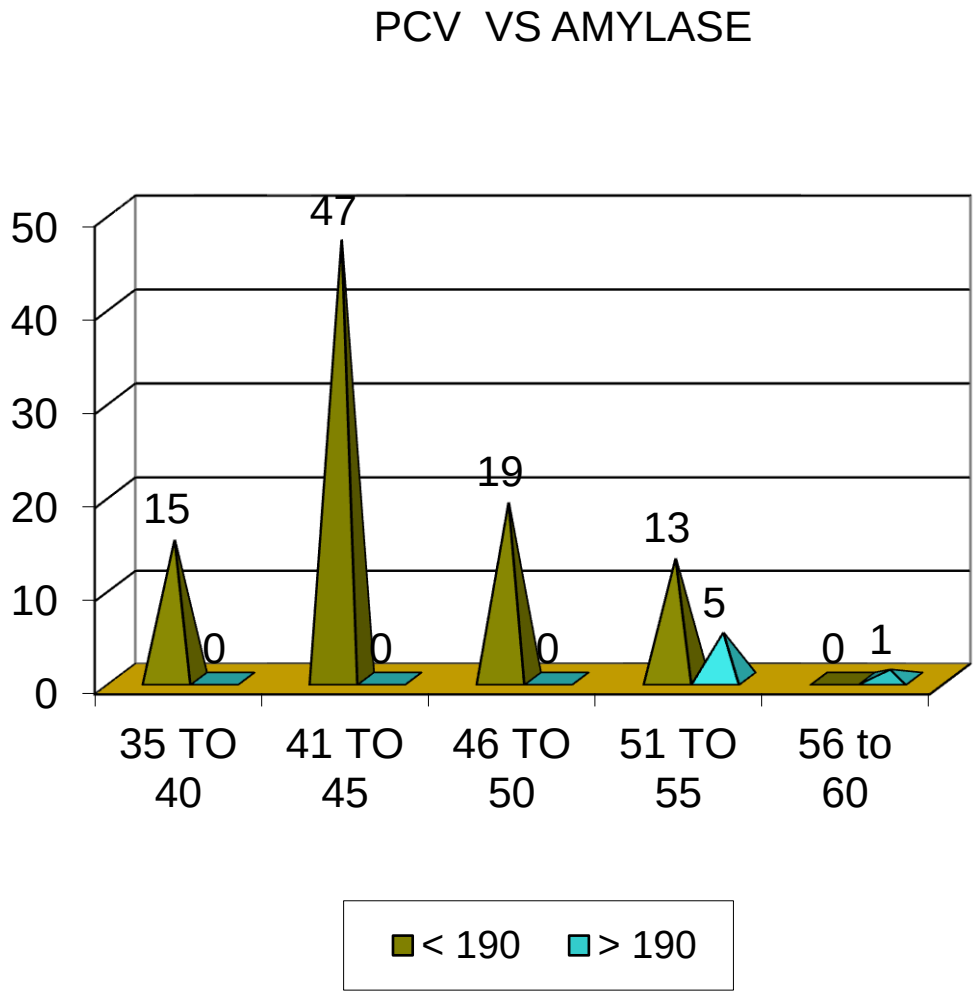


Figure 5.15: association of haematocrit with amylase

PCV	< 190	> 190	
35 TO 40	15	0	
41 TO 45	47	0	
46 TO 50	19	0	
51 TO 55	13	5	0.003 Significant
56 to 60	0	1	
total	94	6	

Table 5.14: association of amylase with haematocrit

Inference:

Raised haematocrit associated with increased amylase, more significant as it has 100% association.

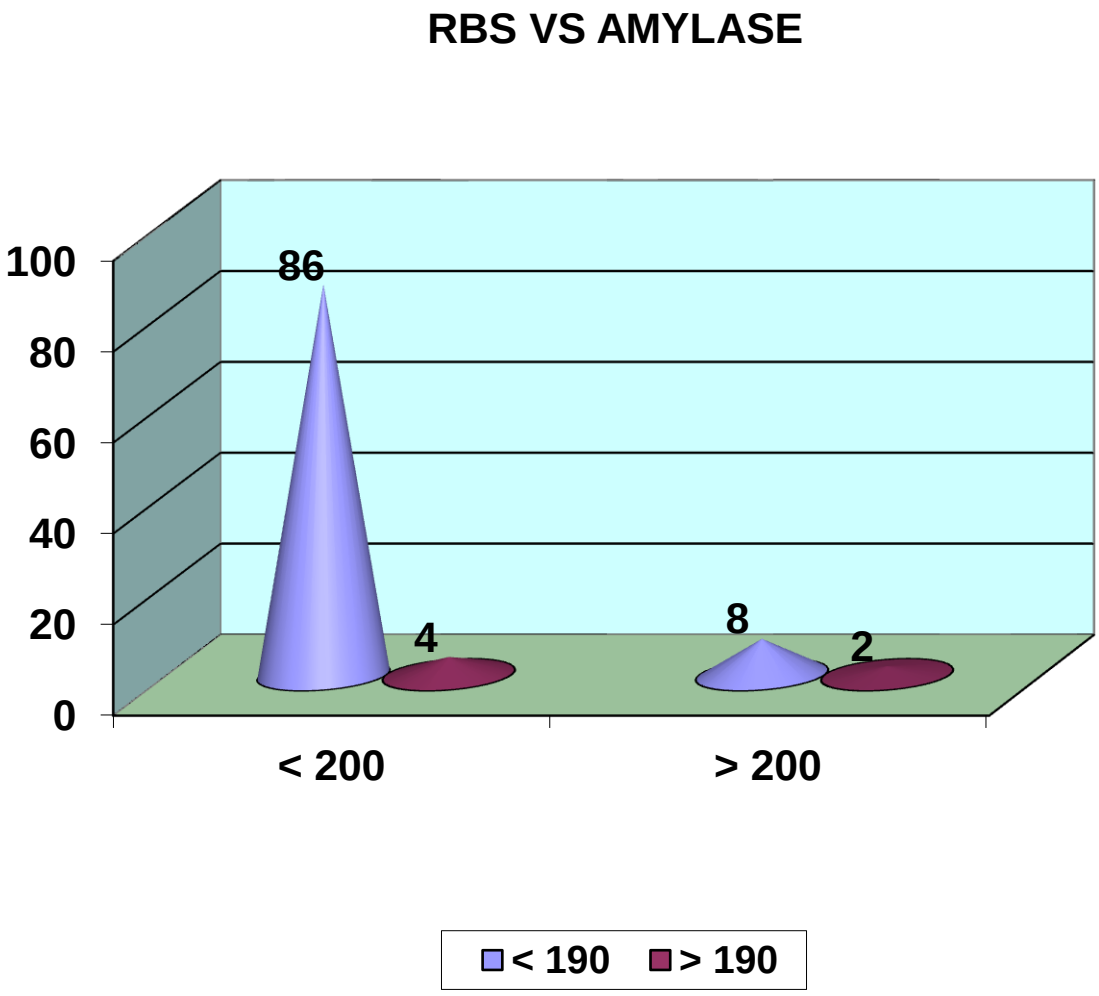


Figure 5.16: association of blood sugar with amylase.

RBS	< 190	> 190	
< 200	86	4	
> 200	8	2	0.878 Not significant
total	94	6	

Table:5.15:association of blood sugar with amylase

Inference:

Out of 10 patients with hyperglyemia 2 patients have associated increased amylase level, not of much significance

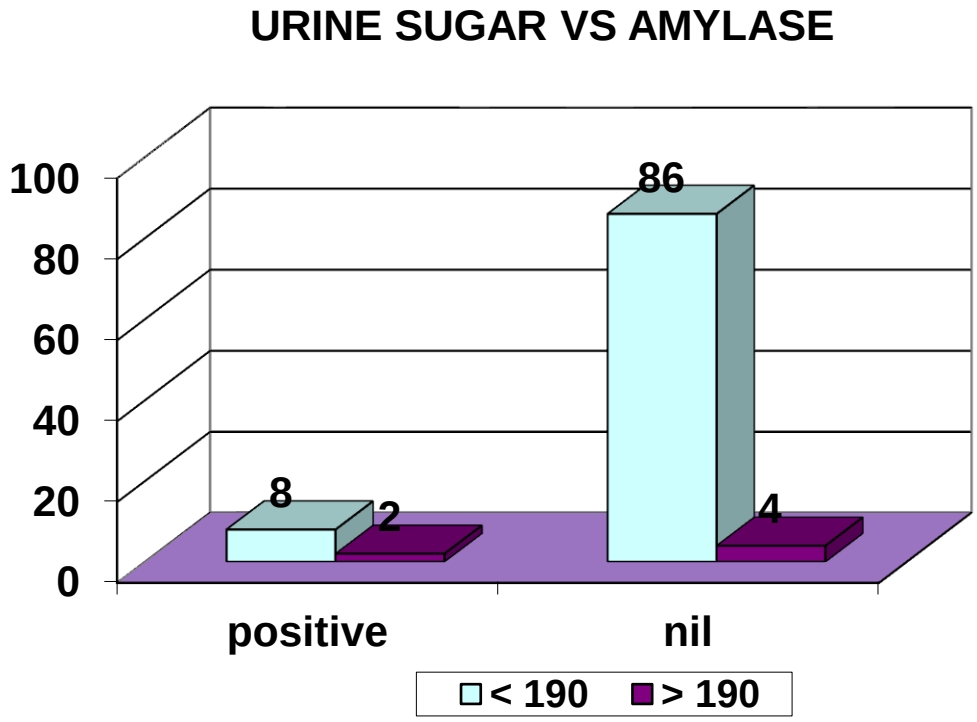


Figure :5.17: association of urine sugar and amylase

Inference:

Out of 6 patients with increased amylase level only 2% have

Glucose in urine , so it is of least significance..

Table 5.16:association of urine sugar and amylase

URINE-SUGAR	< 190	> 190	
positive	8	2	0.324 Not significant
nil	86	4	
total	94	6	

Table 5.17: association of urine acetone with amylase

URINE-ACETONE	< 190	> 190	
positive	1	1	
nil	93	5	0.306 Not significant
total	94	6	

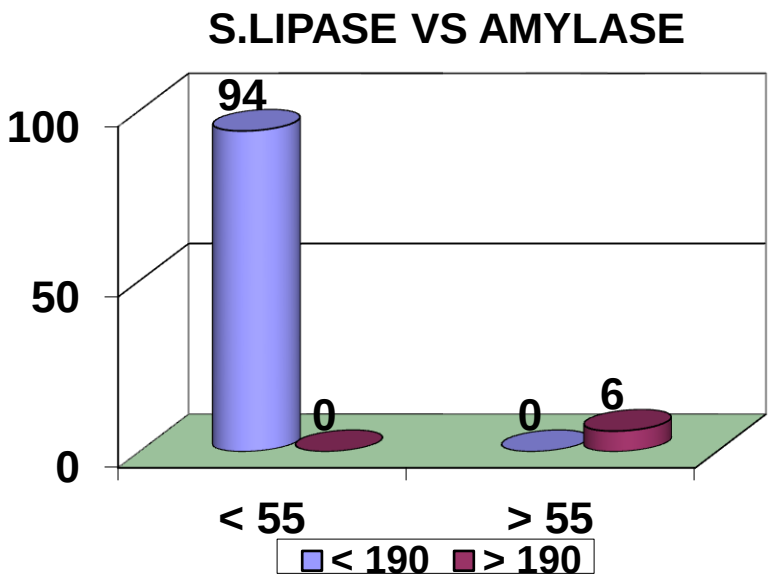


Figure 5.18: association of amylase with lipase

Table 5.17

S.LIPASE	< 190	> 190	
< 55	94	0	0.04 Significant
> 55	0	6	
total	94	6	

Inference:

Increase in amylase level correlates parallel with lipase level , suggestive of pancreatic inflammation ….

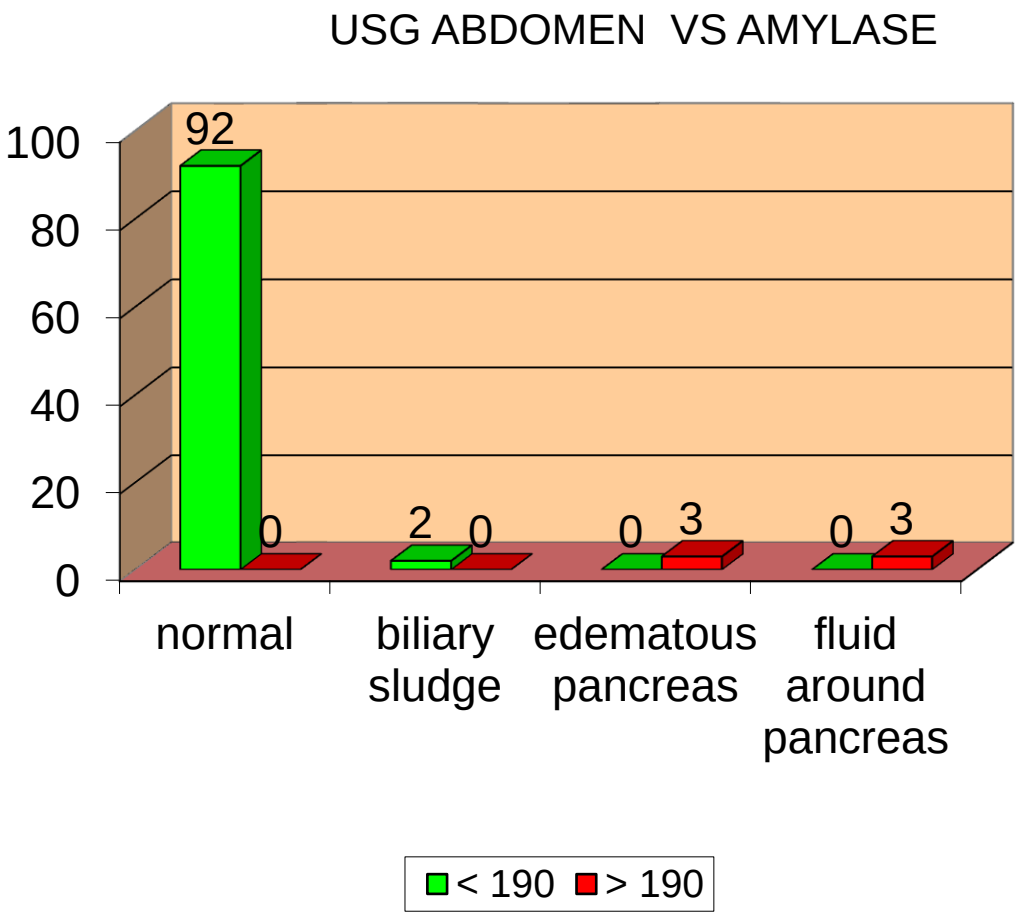


Figure 5.19: relation between amylase and USG-abdomen

Table 5.18: association of USG-abdomen and amylase

USG-ABDOMEN	< 190	> 190	
normal	92	0	0.04 Significant
biliary sludge	2	0	
edematous pancreas	0	3	
fluid around pancreas	0	3	
total	94	6	

Inference:

Increase in amylase level correlates well with USG findings suggestive of pancreatic inflammation..

DISCUSSION

In our study the consumption of OPC poisoning is more among males compared to females

pancreatic enzymes such as amylase, lipase are compared with variables such as age, sex, amount, vitals, need for ventilatory support, random blood sugar, leucocyte count, haematocrit…

This study is to emphasise the importance of diagnosing pancreatitis in unexplained hypotension or shock in OPC excluding other causes also whether the blood sugar elevation correlates with elevation of amylase, suggesting pancreatitis is also the cause for hyperglycemia other than stress hyperglycemia caused by release of stress hormones such as catecholamines which is induced by hyperinsulinemia that occurs during cholinergic phase… paradoxically, studies shows that hypoglycaemia can also occur that cause seizure leading to diagnostic confusion.

As per Dressel and colleagues experiment OPC induced pancreatitis is secondary to functional duct obstruction and stimulated exocrine secretion

In that study hyperglycemia is found in only 7% and glycosuria in 14% .But in our study hyperglycemia is seen in 10% along with glycosuria.

Ketones are found in urine in only 2% , of which 1% is due to starvation ketosis

Remaining 1% is due to hyperglycemic ketoacidosis that present as DKA…

Among the 10% of hyperglycemics , only 2% have evidence of pancreatic Inflammation… pancreatic enzymes are elevated in 6% of the study population Of which only 2% have hyperglycemia which is caused by pancreatic endocrine Insufficiency.

In our study all the 6% of study population have evidence of dehydration and Hemoconcentration evidenced by raised haematocrit which has to be followed up Serially. In any series of study in poisoning and as per our study incidence of OPC poisoning is common among middle aged- men.As per our study, type of compound, amount of compound, doesnot predicted by amylase level.Systolic and diastolic BP does not correlates with amylase level in significant manner, except mild decrease in systolic or diastolic BP Tachycardia in OP poison correlates well with amylase level. In our study study population with amylase > 190 have pulse rate of mean around 95/min.

Respiratory rate if increased is associated with statistically significant increase in amylase level. In our study among 6 patients with hyperamylasemia, 4 patients have increased respiratory rate.Further decreased oxygen saturation have good association with amylase level thus the need for ventilatory support.In our study out of 6 patients having amylase >190 IU/L 4 patients have decreased SPO2 in range of 85 to 90%..

5 out of 6 patients needs ventilator support who have evidence of pancreatic Inflammation…leucocyte count is increased in OPC poisoning irrespective of rise in serum amylase.Finally serum lipase increases parallely with amylase suggesting that other causes of hyperamylasemia are ruled out.

A total of 47 patients were studied in a teaching hospital in Yuzuncu yoi university of which 4 patients have elevated amylase and lipase level around 300U/L and 60U/L…Among patients in which amylase levels between 100-300 U/L Only 2 patients have elevated lipase level, as assessed by calorimetric method..

CONCLUSION:

As per our study incidence of pancreatitis is 6% among OPC poisoning

It is evidenced by increase in serum amylase and lipase , supported by

leucocytosis, increased haematocrit.,USG evidence of pancreatic

inflammation and statistically significant….

The incidence of hyperglycemia is 10% among OPC poisoning

with equal Incidence of glycosuria ...

Relation between blood sugar and pancreatic enzymes in controversial…

out of 6 patients with hyperamylasemia only 2 patients have hyperglycemia..

whether it is due to pancreatitis or stress induced is not known and it is not

statistically significant.

REFERENCES:

1.Pichamuthu K, Jerobin J, Nair A, et al. Bioscavenger therapy for organophosphate poisoning - an open-labeled pilot randomized trial comparing fresh frozen plasma or albumin with saline in acute organophosphate poisoning in humans. Clin Toxicol (Phila). 2010;48(8):813-9.

2. Pazooki S, Solhi H, Vishteh HR, et al. Effectiveness of fresh frozen plasma as supplementary treatment in organophosphate poisoning. Med J Malaysia. 2011;66(4):342-5.

3. Blain PG. (2011). Organophosphorus poisoning (acute). Clin Evid. [Online] Available from www.ncbi.nlm.nih.gov/pubmed/21575287. [Accessed February, 2012].

4. Perera PM, Jayamanna SF, Hettiarachchi R, et al. A phase II clinical trial to assess the safety of clonidine in acute organophosphorus pesticide poisoning. Trials. 2009;10:73.

5. Eddleston M, Juszczak E, Buckley NA, et al. Multiple-dose activated charcoal in acute self-poisoning: a randomised controlled trial. Lancet. 2008;371(9612):579-87.

6. Roberts DM, Buckley N. (2012). Alkalinisation for organo-phosphorus pesticide poisoning. [online] Available from www.onlinelibrary.wiley.com/doi/10.1002/14651858.CD004897.pub2/abstract. [Accessed February, 2012].

7. Blain PG. (2011). Organophosphorus poisoning (acute). Clin Evid. [Online] Available from www.ncbi.nlm.nih.gov/pubmed/21575287 [Accessed February, 2012].

8. Dickson EW, Bird SB, Gaspari RJ, et al. Diazepam inhibits organophosphate-induced central respiratory depression.

9. Chambers JE. Organophosphate compounds an overview. In: Chambers JE, Levi P, eds. Organophosphates: Chemistry, fate and effects. San Diego: Academic Press, 1992:3.17.

10. Krieger RI, ed. Handbook of pesticide toxicology: Principles, 2nd edition. San Diego: Academic Press, 2001.

11. Gupta RC, ed. Toxicology of organophosphate and carbamate compounds. San Diego: Elsevier, 2006.

12. Aldridge WN. Tricresyl phosphates and cholinesterase. Biochem J 1954; 56:185.189.

13. Olsen KR, ed. Poisoning and drug overdose. Stamford, Connecticut: Appleton and Lange, 1998.

14. Olsen KR, ed. Poisoning and drug overdose. Stamford Connecticut; Appleton and Lange, 1998.

15. Committee on Toxicology (COT) of Chemicals in food, consumer products and he environment

organophosphates. Department of Health, 2007.

16. Environmental Protection Agency. Annual Report, 2000. Office of Pesticide Programs. http://www.epa.gov/

oppfead1/annual/2000/2000annual.pdf

17. Environmental Protection Agency. Reregistration Eligibility Decision for Diazinon, 2006. http://www.sps.

gov/pesticides/reregistration/REDS/diazinon_red.pdf

18. European Commission (EC) decision of 6 June 2007 concerning the non inclusion of diazinon in Annex I

to the Council Directive 91/414/EEC and the withdrawal of authorisations for plant protection agents

containing that substance. Official Journal of the European Union 2007; 140:9.10.

19. Australian Pesticides and Veterinary Medicines Authority (APVMA). APVMA suspends the use of diazinon

for sheep dipping and jetting. Media Release, 2007.

20. Department of Primary Industries (DPI) Sheep body lice: Control and eradication. Agriculture Notes of

the DPI State of Victoria, 2007; AG1110.

21. AbouDonia MB, Lapadula DM. Mechanisms of organophosphorusester induced delayed neurotoxicity:

Type I and II. Ann Rev Pharmacol Toxicol 1990; 30:405.440.

22. Lotti M. The pathogenesis of organophosphate polyneuropathy. Crit Rev Toxicol 1992; 21:465.487.

23. AbouDonia MB. Organophosphorus ester induced chronic neurotoxicity. Arch Env Health 2003; 58:484.497.

24. Bishop EL, Stewart HC. Incidence of partial paralysis. Am J Public Health 1930; 20:1307.1312.

25. Zeligs MA. Upper motor neuron sequelae in • gJake • h paralysis: a clinical follow up study. J Nerv Ment Dis

1938; 87:464.470.

26. Richardson RJ, Moore TB, Kayyali US et al. Chlorpyrifos: Assessment of potential or delayed neurotoxicity

by repeated dosing in adult hens with monitoring of brain acetylcholinesterase, brain and lymphocyte

neurotoxic esterase and plasma butyrylcholinesterase activities. Toxicol Sci 1993; 21:89.96.

27. Chow E, Seiber JN, Wilson BW. Isophenos and an in vitro assay for delayed neuropathic potential. Toxicol

Appl Pharmacol 1986; 83:178.183.

28. de Blaquiere GE, Waters L, Blain PG et al. Electrophysiological and biochemical effects of single and

multiple doses of the organophosphate diazinon in the mouse. Toxicol Appl Pharmacol 2000; 166:81.91.

29. Johnson MK. The primary biochemical lesion leading to the delayed neurotoxic effects of some

organophosphorus esters. J Neurochem 1974; 23:785.789.

30. Johnson MK. The target for initiation of delayed neurotoxicity by organophosphorus esters: biochemical

studies and toxicological applications. In: Hodgson E, Bend JR, Philpot RM, Eds. Reviews in Biochemical

Toxicology. New York: Elsevier, 1982; 4:141.212.

31. Minette, PA and PJ Barnes, Muscarinic receptor subtypes in lung. Clinical

implications. Am Rev Respir Dis 1990; 141(3 Pt 2): p. S162-5.

32. Canning, BJ and A Fischer, Neural regulation of airway smooth muscle

tone. Respir Physiol 2001; 125(1-2): p. 113-27.

33. Racke, K and S Matthiesen, The airway cholinergic system: physiology

and pharmacology. Pulm Pharmacol Ther 2004; 17(4): p. 181-98.

34. Chang, FC, RE Foster, ET Beers, DL Rickett, and MG Filbert, Neurophysiological concomitants of soman-induced respiratory depression in awake, behaving guinea pigs. Toxicol Appl Pharmacol 1990; 102(2): p. 233-50.

35. Bird, SB, RJ Gaspari, and EW Dickson, Early death due to severe organophosphate poisoning is a centrally mediated process. Acad Emerg Med 2003; 10(4): p. 295-8.

36. Sungur, M and M Guven, Intensive care management of organophosphate insecticide poisoning. Crit Care 2001; 5(4): p. 211-5.

37. Goswamy, R, A Chaudhuri, and AA Mahashur, Study of respiratory failure in organophosphate and carbamate poisoning. Heart Lung 1994; 23(6): p. 466-72.

38. Tsao, TC, YC Juang, RS Lan, WB Shieh, and CH Lee, Respiratory failure of acute organophosphate and carbamate poisoning. Chest 1990; 98(3): p. 631-6.

39. Binns JH, BC, Bloom F et al, Gulf War Illness and the Health of Gulf War Veterans. Scientific Findings and Recommendations 2008, Veteran's

Affairs: Washington DC. p. 1-465.

40. Page, WF, Long-term health effects of exposure to sarin and other anticholinesterase chemical warfare agents. Mil Med 2003; 168(3): p. 239-45

41. Crouzier, D, VB Le Crom, E Four, G Lallement, and G Testylier, Disruption of mice sleep stages induced by low doses of organophosphorus compound soman. Toxicology 2004; 199(1): p. 59-71.

42. Icenogle, LM, NC Christopher, WP Blackwelder, DP Caldwell, D Qiao, FJ Seidler, TA Slotkin, and ED Levin, Behavioral alterations in adolescent and adult rats caused by a brief subtoxic exposure to chlorpyrifos during neurulation. Neurotoxicol Teratol 2004; 26(1): p. 95-101.

43. Jamal, GA, Neurological syndromes of organophosphorus compounds. Adverse Drug React Toxicol Rev 1997; 16(3): p. 133-70.

44. Eyer, P, Neuropsychopathological changes by organophosphorus compounds--a review. Hum Exp Toxicol 1995; 14(11): p. 857-64.

45. Singh, S and N Sharma, Neurological syndromes following organophosphate poisoning. Neurol India 2000; 48(4): p. 308-13.

46. Damodaran, TV, ST Greenfield, AG Patel, HK Dressman, SK Lin, and MB Abou-Donia, Toxicogenomic studies of the rat brain at an early time point

following acute sarin exposure. Neurochem Res 2006; 31(3): p. 367-81

47. Heard K: The changing indications of gastrointestinal decontamination in poisonings. Clin.Lab Med. 2006; 26: 1-12, vii

48. Greene SL, Dargan PI, Jones AL: Acute poisoning: understanding 90% of cases in a nutshell. Postgrad.Med.J. 2005; 81: 204-16

49. Daly FF, Fountain JS, Murray L, Graudins A, Buckley NA: Guidelines for the management of paracetamol poisoning in Australia and New Zealand--explanation and elaboration. A consensus statement from clinical toxicologists consulting to the Australasian poisons information centres. Med.J.Aust. 2008; 188: 296-301

50. Lam LT: Childhood and adolescence poisoning in NSW, Australia: an analysis of age, sex, geographic, and poison types. Inj.Prev. 2003; 9: 338-42

51. Turner A, Robinson P: Respiratory and gastrointestinal complications of caustic ingestion in children. Emerg.Med.J. 2005; 22: 359-61

52. Fungi poisoning. 1999. Melbourne, State of Victoria. Ref Type: Pamphlet

53. Uhl W, Nolting A, Golor G, Rost KL, Kovar A: Safety of hydroxocobalamin in healthy volunteers in a randomized, placebo-controlled study. Clin.Toxicol.(Phila) 2006; 44 Suppl 1: 17-28

54. Forsyth JC, Mueller PD, Becker CE, Osterloh J, Benowitz NL, Rumack BH et al.: Hydroxocobalamin as a cyanide antidote: safety, efficacy and pharmacokinetics in heavily smoking normal volunteers. J.Toxicol.Clin.Toxicol. 1993; 31: 277-94

55.Borron SW, Baud FJ, Barriot P, Imbert M, Bismuth C: Prospective study of hydroxocobalamin for acute cyanide poisoning in smoke inhalation. Ann.Emerg.Med. 2007; 49: 794-801, 801

56. Houeto P, Hoffman JR, Imbert M, Levillain P, Baud FJ: Relation of blood cyanide to plasma cyanocobalamin concentration after a fixed dose of hydroxocobalamin in cyanide poisoning. Lancet 1995; 346: 605-8

57. Espinoza OB, Perez M, Ramirez MS: Bitter cassava poisoning in eight children: a case report. Vet.Hum.Toxicol. 1992; 34: 65

58. Fortin JL, Desmettre T, Manzon C, Judic-Peureux V, Peugeot-Mortier C, Giocanti JP et al.: Cyanide poisoning and cardiac disorders: 161 cases. J.Emerg.Med. 2010; 38: 467-76

59. Fortin JL, Giocanti JP, Ruttimann M, Kowalski JJ: Prehospital administration of hydroxocobalamin for smoke inhalation-associated cyanide poisoning: 8 years of experience in the Paris Fire Brigade. Clin.Toxicol.(Phila) 2006; 44 Suppl 1: 37-44

60. Borron SW, Baud FJ, Megarbane B, Bismuth C: Hydroxocobalamin for severe acute cyanide poisoning by ingestion or inhalation. Am J.Emerg.Med. 2007; 25: 551-8

61. Pontal PG, Bismuth C, Garnier R: Therapeutic attitude in cyanide poisoning: retrospective study of 24 non-lethal cases. Veterinary and Human Toxicology 1982; 24: 286-7

ABBREVIATION

OPC	-----	organophosphorus compound
AChE	-----	acetylcholinesrerase
BAEM	-----	British association of emergency medicine
CFTR	-----	cystic fibrosis transmembrane regulator
CCK	-----	cholecystokinin
NTE	-----	neuropathy target enterase
OPIDN	-----	organophosphorus induced delayed neuropathy
SWS	-----	swiss cheese protein
PSP	-----	phenyl salygenin phosphate
Hup-A	-----	Huperzine-A
MAP	-----	mitogen activated protein
DFP	-----	Diisopropylphosphorofluoridate
PTEs	-----	phosphotriesterase
TLC	-----	thin layer chromatography
GABA	-----	gamma amino butyric acid

PROFORMA

NAME: AGE: SEX: DATE:

PRESENTING COMPLAINTS:

PAST HISTORY:

H/O CHRONIC PANCREATITIS/ PANCREATIC PROCEDURES / ALCOHOLISM / DRUG INTAKE / DM

GENERAL EXAMINATION:

VENTILATORY SUPPORT: YES / NO

IF YES, VENTILATORY SETTINGS:

VITALS: PULSE: BP: RESPIRATORY.RATE: SpO2:

SYSTEM EXAMINATION:

CVS:

RS:

ABD:

CNS:

INVESTIGATIONS:

TOTAL LEUCOCYTE COUNT:

CASUAL BLOOD SUGAR: SERUM. AMYLASE: SERUM.LIPASE:

URINE ACETONE: URINE SUGAR: PCV:

USG-ABDOMEN:

MASTER CHART

SL.NO	NAME	AGE	SEX	COMPOUND	AMOUNT	BP mmHg	PULSE/mi	RR/min	SPO2 %	ventilato	TC	PCV	RBS	URINE-SUGAR	URINE-ACET	S.AMYLAS	S.LIPASE	USG-ABDOMEN
1	ANTONY	55Y	M	propaphenar	>5q	100/60	98	18	96	no	6700	44	126	nil	nil	58	22	normal
2	ALBERT	34Y	M	propaphenar	<5q	120/70	62	14	95	no	7700	45	167	nil	nil	141	32	normal
3	ESAKIPANDI	40Y	M	propaphenar	>5q	120/90	68	13	95	no	6700	46	64	nil	nil	78	33	normal
4	MURUGAPERUMA	28Y	M	propaphenar	>5q	110/70	72	18	96	no	15,900	44	156	nil	nil	86	22	normal
5	SURESH KUMA	28Y	M	monocrotaphar	>5q	150/100	125	22	90	yes	17000	54	155	nil	nil	54	18	normal
6	BALAMMAL	48Y	M	PHORATE-10G	>5q	100/60	105	22	88	yes	19300	56	369	paritive	paritive	269	65	edematous pancreas
7	GAJENDRAN	36Y	M	quinalphar	>5q	140/90	102	20	90	yes	9300	45	122	nil	nil	56	16	normal
8	CHELLADURAI	32Y	M	monocrotaphar	<5q	120/70	64	14	98	no	12000	42	75	nil	nil	44	14	normal
9	THANGAMMAL	44Y	F	parathion	>5q	90/60	124	24	88	yes	15500	55	260	paritive	nil	496	56	fluid around pancreas
10	NAMBI	27Y	M	quinalphar	<5q	140/90	68	14	98	no	9700	42	112	nil	nil	56	16	normal
11	DURAIRAJ	35Y	M	monocrotaphar	>5q	190/110	54	12	90	yes	6700	52	78	nil	nil	35	14	normal
12	MADASAMY	55Y	M	propaphenar	>5q	130/70	66	16	97	no	13650	45	164	nil	paritive	126	42	biliary sludge
13	PANDARAM	36Y	M	monocrotaphar	>5q	120/80	52	14	92	yes	5400	54	122	nil	nil	102	16	normal
14	MUTHU	33Y	M	propaphenar	>5q	110/60	76	16	98	no	8800	46	144	nil	nil	98	24	normal
15	RAMASAMY	45Y	M	quinalphar	>5q	120/80	78	13	96	no	12870	38	68	nil	nil	44	12	normal
16	ALICE	26Y	F	dimethoate	>5q	100/70	98	24	89	yes	12050	54	206	paritive	nil	56	14	normal
17	PARAMESHAR	32Y	F	monocrotaphar	<5q	120/90	98	18	98	no	4500	45	144	nil	nil	78	22	normal
18	RAMAKRISHNA	36Y	M	propaphenar	>5q	110/70	68	12	95	no	12260	54	156	nil	nil	96	28	normal
19	THANGAM	27Y	F	quinalphar	>5q	160/100	106	24	92	yes	14700	50	178	nil	nil	123	33	normal
20	THIAGARAJAN	36Y	M	monocrotaphar	>5q	170/90	98	22	90	yes	12000	52	146	nil	nil	112	22	normal
21	MAYILVAGANA	35Y	M	quinalphar	>5q	120/80	56	12	94	no	6500	37	76	nil	nil	54	12	normal
22	SURESH	24Y	M	propaphenar	>5q	110/70	66	14	97	no	13070	42	86	nil	nil	58	16	normal
23	MANGATHAL	42Y	F	dimethoate	<5q	130/80	72	16	96	no	8700	46	144	nil	nil	65	18	normal
24	SENTHIL	28Y	M	propaphenar	>5q	120/90	64	12	97	no	9800	44	156	nil	nil	58	22	normal
25	ABDUL	26Y	M	dimethoate	>5q	110/80	66	14	96	no	11000	45	154	nil	nil	68	14	normal
26	ANNAMALAI	32Y	M	dimethoate	>5q	100/60	102	24	88	yes	12000	54	234	paritive	nil	98	24	normal
27	SUBBIAH	45Y	M	quinalphar	<5q	130/80	88	16	97	no	13200	46	118	nil	nil	48	22	normal
28	MASANAM	36Y	F	propaphenar	>5q	150/90	64	14	96	no	6700	42	128	nil	nil	56	12	normal
29	MUTHLINGAM	32Y	M	dimethoate	>5q	100/70	98	20	95	no	11000	46	156	nil	nil	76	21	normal
30	SAMUVEL	27Y	M	diazinon	>5q	100/60	56	12	93	yes	17800	54	186	nil	nil	296	56	edematous pancreas
31	RAMARAJAN	36Y	M	propaphenar	>5q	130/80	68	15	96	no	8700	38	387	paritive	nil	76	28	normal
32	ARUMUGAM	33Y	M	monocrotaphar	>5q	170/90	96	15	97	no	6700	46	128	nil	nil	87	12	normal
33	PERUMAL	29Y	M	dimethoate	<5q	140/90	54	12	96	no	12000	44	126	nil	nil	58	14	normal
34	KANNAN	28Y	M	propaphenar	>5q	190/110	124	24	90	yes	13890	52	186	nil	nil	422	66	fluid around pancreas
35	NAINAR	36Y	M	monocrotaphar	>5q	140/80	66	16	97	no	12870	43	156	nil	nil	122	22	normal
36	CHANDRAN	44Y	M	propaphenar	>5q	120/70	64	14	98	no	7800	39	145	nil	nil	76	32	normal
37	LAKSHMI	27Y	F	quinalphar	<5q	110/70	54	18	96	no	6400	39	134	nil	nil	54	23	normal
38	SARASWATHI	34Y	F	dimethoate	>5q	120/90	94	19	92	yes	11000	42	156	nil	nil	56	21	normal
39	JEYARAMAN	42Y	M	monocrotaphar	<5q	110/80	58	16	98	no	8900	40	98	nil	nil	44	16	normal
40	NAGARAJAN	36Y	M	propaphenar	>5q	140/80	76	14	96	no	11280	42	156	nil	nil	86	24	normal
41	KALI	56Y	M	malathion	>5q	170/100	96	23	90	yes	22000	52	216	paritive	nil	134	42	normal
42	SUDALAI	34Y	M	monocrotaphar	>5q	100/70	102	20	88	yes	14500	48	156	nil	nil	96	34	normal
43	MURUGAN	42Y	M	dimethoate	>5q	160/90	76	18	97	no	9700	46	134	nil	nil	48	18	normal
44	MANIKARAJ	42Y	M	propaphenar	<5q	130/80	78	14	98	no	6500	42	145	nil	nil	56	34	normal
45	ARUNRAJ	27Y	M	quinalphar	>5q	160/90	56	12	96	no	8600	44	167	nil	nil	58	32	normal
46	PACKIYAM	36Y	F	PHORATE-10G	>5q	90/60	122	22	89	yes	11000	52	134	nil	nil	98	32	normal
47	GNANAM	32Y	M	monocrotaphar	>5q	140/70	76	16	97	no	6500	42	122	nil	nil	102	30	normal
48	JEYARAMAN	36Y	M	propaphenar	>5q	130/90	92	16	96	no	12860	48	78	nil	nil	58	16	normal
49	PITCHAI	42Y	M	quinalphar	>5q	90/70	108	22	92	yes	13460	51	167	nil	nil	68	22	normal
50	PARVATHY	28Y	F	monocrotaphar	<5q	140/80	58	14	98	no	7500	39	156	nil	nil	56	18	normal

50	PARVATHY	28Y	F	monocratopha	<5q	140/80	58	14	98	no	7500	39	156	nil	nil	56	18	normal
51	PAULKANI	32Y	F	dimethoate	<5q	110/80	68	16	97	no	8600	39	145	nil	nil	58	18	normal
52	KANMANI	29Y	F	quinalphar	>5q	130/70	76	19	96	no	12000	41	156	nil	nil	88	34	normal
53	RAMESH	24Y	M	propaphenar	>5q	150/80	88	18	95	no	8700	42	152	nil	nil	54	23	normal
54	RAMAR	32Y	M	quinalphar	>5q	130/60	76	14	98	no	9800	45	98	nil	nil	58	22	normal
55	VADIVEL	45Y	M	monocratopha	>5q	110/60	58	12	96	no	8700	46	146	nil	nil	68	32	normal
56	RAJA	36Y	M	malathion	>5q	150/70	98	18	90	yes	12060	52	277	paritive	nil	118	34	normal
57	ESAKI	46Y	M	monocratopha	<5q	120/90	56	13	95	no	6700	45	165	nil	nil	96	32	normal
58	MEENAKSHI	28Y	F	diazinon	<5q	110/60	74	18	92	yes	12890	43	132	nil	nil	44	30	normal
59	RANI	26Y	F	dimethoate	<5q	100/70	98	20	95	no	9760	44	145	nil	nil	78	24	normal
60	KARTHIK	29Y	M	propaphenar	>5q	170/90	76	15	96	no	13760	51	98	nil	nil	76	23	normal
61	RAMAN	42Y	M	quinalphar	>5q	160/80	58	16	97	no	11560	45	157	nil	nil	72	22	normal
62	VISHNU	56Y	M	monocratopha	>5q	100/70	78	18	92	yes	12860	44	156	nil	nil	58	32	normal
63	THOMAS	28Y	M	quinalphar	<5q	120/80	56	13	97	no	6890	46	134	nil	nil	68	14	normal
64	THIRUVALAN	34Y	M	parathion	>5q	110/60	54	16	98	no	16660	52	66	nil	nil	416	68	edemalous pancreas
65	MUTHURAM	36Y	M	quinalphar	>5q	100/70	66	18	97	no	12460	44	78	nil	nil	68	31	normal
66	MUTHUKUMAR	26Y	M	monocratopha	>5q	120/70	98	22	95	no	11560	46	145	nil	nil	46	21	normal
67	MICHAEL	29Y	M	parathion	<5q	100/60	98	14	97	no	7700	41	132	nil	nil	96	22	normal
68	MYDEEN	45Y	M	propaphenar	>5q	160/90	92	24	92	yes	13450	48	176	nil	nil	54	21	biliary sludge
69	RAJAKANI	54Y	F	quinalphar	<5q	100/70	52	14	95	no	6580	40	134	nil	nil	56	24	normal
70	THANGAM	52Y	M	monocratopha	>5q	150/80	86	18	98	no	7800	45	278	paritive	nil	68	24	normal
71	MADHAVAN	42Y	M	propaphenar	>5q	180/90	56	16	97	no	8700	47	168	nil	nil	98	18	normal
72	MOHAN	34Y	M	dimethoate	<5q	140/90	56	14	98	no	9860	46	125	nil	nil	76	19	normal
73	AKBAR	36Y	M	quinalphar	>5q	130/90	76	18	95	no	11870	43	156	nil	nil	56	21	normal
74	SIVAGAMI	28Y	F	monocratopha	<5q	120/70	64	16	96	no	12330	42	124	nil	nil	58	14	normal
75	SUDAGAR	34Y	M	propaphenar	>5q	90/70	108	24	88	yes	12480	52	176	nil	nil	256	56	fluid around pancreas
76	SUNIL	27Y	M	diazinon	<5q	130/70	98	22	96	no	7800	41	113	nil	nil	56	16	normal
77	PACHAI	24Y	M	monocratopha	>5q	100/70	134	26	90	yes	17800	49	267	paritive	nil	58	18	normal
78	PETER	34Y	M	quinalphar	>5q	120/80	54	14	98	no	7680	41	134	nil	nil	78	24	normal
79	VELAYUTHAM	45Y	M	monocratopha	>5q	130/90	58	17	97	no	11280	42	143	nil	nil	58	14	normal
80	PERUMAL	56Y	M	propaphenar	>5q	110/70	70	18	96	no	6580	40	156	nil	nil	78	19	normal
81	PILLAI	45Y	M	quinalphar	<5q	130/70	64	14	97	no	7700	45	164	nil	nil	56	16	normal
82	VENKETESH	29Y	M	PHORATE-10G	>5q	100/70	98	22	92	yes	8600	49	288	paritive	nil	98	34	normal
83	SANKAR	29Y	M	propaphenar	<5q	110/70	56	13	97	no	8900	42	128	nil	nil	54	21	normal
84	TAMILSELVI	28Y	F	monocratopha	>5q	130/80	68	19	98	no	12660	44	145	nil	nil	52	16	normal
85	PACKIYAM	34Y	F	quinalphar	>5q	160/90	112	24	92	yes	12460	42	127	nil	nil	67	23	normal
86	RAGHAVAN	37y	M	propaphenar	>5q	150/90	92	18	96	no	6500	39	89	nil	nil	44	21	normal
87	PANIMALAR	26Y	F	propaphenar	<5q	120/80	56	14	97	no	9870	39	66	nil	nil	56	14	normal
88	SIVAN	52Y	M	quinalphar	>5q	170/100	66	18	95	no	11000	42	75	nil	nil	88	18	normal
89	SELVARAJ	34Y	M	monocratopha	>5q	160/90	76	14	99	no	14580	44	156	nil	nil	89	17	normal
90	AANAND	26Y	M	monocratopha	>5q	140/80	72	18	96	no	13670	45	167	nil	nil	88	22	normal
91	PETCHI	35Y	F	propaphenar	<5q	110/70	68	14	97	no	8960	39	126	nil	nil	58	14	normal
92	PAPPA	38Y	F	quinalphar	>5q	90/70	112	27	91	yes	15600	45	167	nil	nil	78	34	normal
93	GURUSAMY	28Y	M	propaphenar	>5q	100/70	58	14	98	no	6500	42	112	nil	nil	44	12	normal
94	PALANIVEL	32Y	M	propaphenar	>5q	110/80	56	16	97	no	7600	42	66	nil	nil	42	13	normal
95	VELU	35Y	M	monocratopha	<5q	120/80	68	14	98	no	12860	48	68	nil	nil	57	24	normal
96	SAMY	44Y	M	quinalphar	>5q	140/80	72	16	95	no	4500	38	112	nil	nil	68	21	normal
97	KULANDHAI	36y	M	dimethoate	<5q	110/70	66	14	96	no	13800	44	134	nil	nil	78	22	normal
98	MUNUSAMY	45Y	M	propaphenar	>5q	130/90	108	20	94	yes	12670	52	167	nil	nil	134	34	normal
99	ARULSELVI	26Y	F	monocratopha	<5q	120/70	56	14	97	no	6500	39	123	nil	nil	76	23	normal
100	WASIM	39y	M	quinalphar	>5q	160/90	76	17	98	no	13890	45	145	nil	nil	56	31	normal